RANDOMISED TRIALS IN CHILD HEALTH IN DEVELOPING COUNTRIES

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Please send suggestions about this booklet to:

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SEARCH STRATEGY

Pubmed Advanced strategy, search: ((Developing countries; Developing country; Countries, developing; Developed countries; Country, developing; Countries, developed; Developed country; Country, developed; Nations, developing; Developing nations OR India OR Africa OR Asia OR South America OR Papua New Guinea OR Asia-Pacific) and (Child*)) AND (randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract])) publication date between July 1st 2012 and June 30th 2013.

Introduction

This booklet is compiled annually to summarize the evidence on child health derived from randomized or controlled trials in developing countries over the previous year. The aim is to make this information widely available to paediatricians, nurses, other health workers and administrators in resource poor settings where up-to-date information is hard to find. It is hoped that such information will be helpful in reviewing treatment policies, clinical practice and public health strategies.

The method of searching for studies to include uses PubMed, a search engine that is freely available and widely used in most countries throughout the world. The search strategy has been chosen to capture as many relevant studies as possible, although it is possible that I have missed some. If you know of a relevant RCT or meta-analysis that has not been included in this year's review, please let me know. The search strategy is reproducible by anyone with access to the Internet, through http://www.ncbi.nlm.nih.gov/sites/entrez

Randomized controlled trials (RCTs) are far from the only valuable scientific evidence, and some RCTs, because of problems with design or implementation have limited value. However the method of the Randomized Trial is the Gold Standard for determining attributable benefit or harm from clinical and public health interventions. When done properly they eliminate bias and confounding. However their results should not be accepted uncritically and they should be evaluated for quality and validity. Before the result of an RCT can be generalized to another setting there must be consideration of the wider applicability, feasibility and potential for sustainability.

This year 197 studies were identified. These came from all regions of the world, mostly from developing country researchers. Several trials from 2013-14 will lead to significant changes in child health approaches or clinical recommendations.

We have included the web-link for 96 papers that are available in full-text on the Internet free of charge. More importantly, through HINARI (http://www.who.int/hinari/en/) a program set up by WHO in collaboration with major publishers, the full-text versions of over 13,000 journal titles and 29,000 e-books are now available to health institutions in over 100 countries. If your health institution (medical school, teaching hospital, nursing school, government office) has not registered with HINARI, you can check your eligibility and register online.

Please feel free to distribute this booklet to any colleagues. The revious editions (2002-2013) are available at: www.ichrc.org

We recently published a summary of the previous 11 years of the controlled trials. The reference for this is: Duke T, Fuller D. Arch Dis Child 2014, 99:615–620, and you may download it at: **http://adc.bmj.com/content/99/7/615.full.pdf+html**

In 2013-14 three trials reported significant reductions in mortality (marked with *** in the booklet)**:**

- In children with severe malaria from rural villages in Ghana, Tanzania and Bangladesh, administration of rectal artesunate by village health workers prior to referral reduced mortality (but increased mortality in adults). This was a systematic review of previously published trials.

- In a pilot study in Vietnam and Taiwan of the treatment of brain-stem encephalitis, the most severe form of Enterovirus 71 infection, use of milrinone reduced mortality at one week of treatment (and studies in China the Enterovirus 71 vaccine provided effective antibody responses and clinical protection against hand, foot and mouth disease, the common milder manifestation of the same virus).
- In children managed in an intensive care unit in India, targeting therapy to achieve a certain cerebral perfusion pressure (mean blood pressure - intracranial pressure) was associated with lower mortality than targeting therapy merely to reducing inctracranial pressure.

A brief summary of some of the important results in 2013-14

- In an urban re-settlement community in Delhi, India, short-course prophylactic zinc supplementation for 2 weeks reduced diarrhoea morbidity in infants of 6 to 11 months for up to 5 months.
- In contrast to an earlier trial in Zanzibar, in Ghana malaria incidence was significantly lower in children receiving micronutrient powder with iron compared with children receiving micronutrient powder and no iron.
- In Brazil the fortification of drinking water with iron and ascorbic acid (vitamin C) in schools improved children's haemoglobin and mean corpuscular volume
- The results are mixed for probiotics: In 2 studies of children with diarrhoea from India, Lactobacillus GG given for five days reduced the duration of diarrhoea, and when the pro-biotic was given for 4 weeks there was reduced recurrence of rotavirus diarrhoea. In Thailand use of probiotics for diarrhoea reduced hospital length of stay, but there was no difference in duration of diarrhoea. Among HIV-infected or exposed premature neonates in South Africa, probiotics did not increase feed tolerance or weight gain.
- Intrarectal diazepam was more effective in stopping acute seizures in children in the Democratic Republic of Congo than sub-lingual lorazepam
- In term and near-term neonates in India, phenobarbitone was more effective than phenytoin in controlling seizures, regardless of the cause.
- Early initiation of ART in HIV-positive children improved quality of life compared with delayed treatment based on CD4 count
- In HIV infected children in Uganda and Zimbabwe continuing cotrimoxazole prophylaxis reduced the risk of malaria, and hospitalisation with other infections (pneumonia, sepsis, meningitis).
- In HIV infected children in Uganda and Zimbabwe rates of bacterial infection decreased markedly in the first 12 months after commencing ART.
- In South African children with HIV, multiple micronutrient supplementation improved weight-for-height, and reduced diarrhoea and acute respiratory infections.
- In a South African township a program of pregnancy and post-natal home visits was associated with improved infant breastfeeding and all anthropomorphic indices of growth.
- In Uganda when nurses and peer support women provided post delivery care for women with HIV on ART there was no greater increase in treatment failure than when that care was provided by physicians.

- Studies of school-based programs to reduce soil-based helminth infections in Sri Lanka, the Peruvian Amazon, Kenya and China showed reductions in some species of worm infestation, and that children's knowledge of hygiene was improved. In schools in Kenya the effect of improved sanitation and water supply improvements, in addition to deworming, seemed to be the most effective against Ascaris lumbricoides, and less against hookworm and Trichiuris. In the only school-based trial this year which assessed haemoglobin level or school performance (in Sri Lanka), there was no effect of a program to reduce soil-based helminth infections.
- In seriously ill Indian children with central nervous system infection, use of 0.9% saline and 5% dextrose significantly reduced the risk of hyponatraemia compared to intravenous fluids containing 77mmol/L or 30mmol/L.
- Among Indian children with chronic kidney disease, enalapril reduced proteinuria, and among Thai children with chronic kidney disease the treatment of vitamin D deficiency reduced the dose of erythropoietin required.
- In children in Kenya and Uganda with uncomplicated malaria, artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) remained effective, with almost 100% of children having parasite clearance at 3 days (in Uganda); although in Kenya sub-microscopic rersidual parasitaemia occurred in about 30%. Delayed parasite clearance with AL was reported from Asia.
- Several trials of dihydroartemisinin-piperaquine this year. In a meta-anlysis of trials in African children there was a consistently lower recurrence risk of malaria at 28 days in children treated with DP compared with AL, reflecting the longer half-life of piperquine than lumefantrine.
- In Indonesian children with uncomplicated vivax malaria, a regimen of DP and primaquine (0.25mg/kg) was effective, with an intravascular haemolysis rate of 1.5% in un-selected patients (a known side-effect of primaquine). In a meta-analysis of treatment trials in Asia and Oceanea, DP had a more sustained effect against *P. vivax* than AL, whether primaquine was given or not.
- In Zanzibar, reminders by mobile phone text-messages increased the proportion of women attending antenatal clinics
- In Gambia, vitamin D supplementation taken by women in the third trimester of pregnancy increased linear growth in the first year of their baby's life, while in Burkina Faso the use of prenatal lipid nutrient supplements by pregnant women did not improve infant growth. However in Bangladesh pre-natal micronutrient supplementations reduced growth in the first 54 months among exclusively breast-fed infants (the MINIMat trial).
- A systematic review showed that children with measles who receive antibiotics are less likely to develop complications, particularly pneumonia, purulent otitis media and tonsillitis.
- In Malawi, HIV was found not to be an independent cause of pre-term birth.
- In urban and rural children in Pakistan, micronutrient powder containing iron, with or without zinc reduced iron-deficiency anaemia, but was associated with increased risk of diarrhoea. Also in Indian children given folic acid or folic acid and B12 supplementation, there was an increased risk of persistent diarrhoea, and no benefit on ARI morbidity

- Use of the new complimentary feeding guidelines which emphasise the use of red meat and daily fruit and vegetables lead to an increase in haemoglobin, but no difference in linear growth or zinc levels
- In Kenyan schools supplemental feeding programs involving animal source proteins (meat or milk) increased cognitive performance and reduced infectious disease morbidity.
- In children in India with orbital cellulitis, oral prednisolone as an adjunct to intravenous antibiotics lead to more rapid resolution of symptoms and signs and more rapid improvement in visual acuity
- In Tanzania annual mass drug administration (MDA) with topical tetracycline for infants <6 months and oral azithriomycin for older children reduced trachoma incidence increasingly with each annual campaign.
- In Kolkata, oral cholera vaccine provided sustained protection against cholera, with cumulative efficacy of 65% at 5 years. Previously, long-term efficacy of oral cholera vaccine had not been demonstrated.
- In trials in Brazil and Malaysia, the Dengue vaccine CYD-TDV elicited humoral immune responses against all 4 dengue serotypes. Geometric mean titres of antibodies increased by 4-8-fold from baseline after the third vaccine dose.
- In Malaysian children with a high prevalence of iron deficiency anaemia, a single dose of vitamin A 200,000 U, along with iron supplementation, reduced iron deficiency anaemia significantly more than iron supplementation alone.
- In public primary schools in Andrah Pradesh, India, supplementary, remedial teaching and learning materials had a beneficial effect on language and mathematics test scores for children in classes two, three and four. Better quality education improves learning outcomes!
- In trials in Ecuador and Tanzania, zinc sulphate as adjuctive treatment for pneumonia did not hasten resolution of clinical disease
- In Lao PDR, use of topical insect repellents did not help to prevent malaria in families that were also using long-lasting insecticide treated bed-nets
- In Burkina Faso prenatal lipid nutrient supplements did not improve infant growth

Many studies this year had small sample sizes; the terms or phrases: ‘no difference’, non-inferiority, and equivalence were used in some papers with insufficient consideration to the possibility of a type II error. This can be misleading, and lead to the discarding of an effective intervention, or numerous inadequate trials of the same intervention.

Randomised trials often report the “average effect”, that is the effect on the overall population. However, depending on how specifically that population is defined, within that population may be children who will benefit from the therapy or intervention, children for whom the therapy will have no effect, and some children for whom it may be harmful. The “average” of these effects may be “no overall effect”, but it is increasingly important that researchers try to understand the effects for individuals or sub-groups within trials, and the context in which benefit or not occurs.

Some of the context differences that influence the results may include: individual or population characteristics, comorbidities; the health care environment and health care providers;

geographical factors; other interventions; the delivery mechanism for the drug, vaccine or other intervention; the disease stage and specific aetiology; economic, social and cultural characteristics of the population and individuals within it…and other unknown factors. This can be even more complex in understanding systematic reviews of randomised trials (where heterogeneity is often reported incompletely).

Incorporating a detailed understanding of effect in context requires a nuanced approach to clinical trials, and the randomised design may not be the best method for all interventions. This is especially the case for complex interventions (i.e. a complex clinical therapy or a health system improvement program)

In the last 12 years there have been 1750 trials summarised in the various editions of this booklet. The public health benefits that have come from the huge number of trials on malaria, for example can be seen in the uptake of new interventions and reductions in malaria in each affected country in the world. The funding of comprehensive programs of research to "roll-back" malaria and implement the results of trials is a good example of the optimum benefit of research. The changes to HIV treatment is another example of public health which has benefited remaekably from randomised trials: the changing improvements to prevention of parent-to-child transmission being a primary example. While malaria and HIV rates are falling reductions of the same magnitude are not being seen in pneumonia, malnutrition or neonatal illness – and taking similar comprehensive approaches to the research agenda and to research-driven public health interventions are needed.

It is encouraging to see the increased evaluation of the developmental effects of interventions, especially in populations at risk of developmental problems such as HIV. Also encouraging is to see the increased trials among adolescents, trials of school-based health and improvements in education.

In 2013-14 showed further the impact of economic transition, Western morbidities and high-technology research, with clinical trials this year from India and China on issues related to non-communicable diseases, including obesity, oral health, cancer, allergy, and modifying risk factors in childhood for adult cardiovascular disease.

More support is needed for developing public health research capacity in the poorest countries. The flourishing research output from China, India and other transitional countries is a welcome trend, but may mean that the health issues in the poorest nations with the highest child mortality burdens are over-shadowed, despite the overall increase in the number of trials. Ongoing eforts to reduce inequity in child health are especially important beyond 2015, and this will be served by appropriate research.

Trevor Duke
July 2014

Acknowledgement
Many thanks to Eleanor Neal and Rosie Duke, for their invaluable editorial assistance.

Acute respiratory infection

(See also Zinc, Pneumococcal vaccine, Hygiene and environmental health)

Treatment of non-severe pneumonia

Int J Prev Med. 2013 Oct;4(10):1162-8.

Clinical Effectiveness of Co-trimoxazole vs. Amoxicillin in the Treatment of Non-Severe Pneumonia in Children in India: A Randomized Controlled Trial.

Rajesh SM[1], Singhal V.

[1]Department of Pediatrics, Kasturba Medical College, Manipal University, Mangalore, Karnataka, India.

BACKGROUND:
Acute respiratory infection (ARI) in young children is responsible for an estimated 4.1 million deaths worldwide of which approximately 90% are due to pneumonia. To study the clinical effectiveness of co-trimoxazole versus amoxicillin in the treatment of non-severe pneumonia, as defined by WHO, in children in the age group of 02 months to 5 years. Randomized Control Trial study was conducted in out patient department of a large tertiary care hospital after taking consent from parents and ethical committee clearance.

METHODS:
Children in study group were treated with amoxicillin (40 mg/kg/day in 3 divided doses) and those in control group were treated with co-trimoxazole (8 mg/kg/day of trimethoprim in 2 divided doses). All cases were reviewed on second and fifth day. The effectiveness and therapy failure were decided on the basis of clinical, radiological and complete blood count results.

RESULTS:
Two hundred and four cases of non severe pneumonia were studied. All cases were diagnosed on the basis of clinical criteria, as defined by WHO. **Treatment failure was seen in 8.09% cases with amoxicillin and 39.05% cases with co-trimoxazole.** Cost of one complete course with amoxicillin was 2.3 times higher than with co-trimoxazole. Compliance of therapy to co-trimoxazole (90.47%) was better than to amoxicillin (83.84%).

CONCLUSIONS:
The response to treatment with amoxicillin is faster, however, compliance is slightly poorer and cost of treatment high. In order to improve the compliance, better counseling and more studies are required to ascertain the efficacy of amoxicillin in higher dosage over a shorter period of time.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24319556/

Comment
This has implications for the interpretation of some community-based antibiotic trials, which found no difference between community-based care (using amoxicillin) and given standard antibiotic, which was cotrimoxazole, and then referred to hospital (Soofi S, et al, Lancet 2012).

Zinc for treatment of pneumonia

Am J Clin Nutr. 2014 Mar;99(3):497-505. doi: 10.3945/ajcn.113.067892. Epub 2014 Jan 15.

Zinc as an adjunct to the treatment of severe pneumonia in Ecuadorian children: a randomized controlled trial.

Sempértegui F, Estrella B, Rodríguez O, Gómez D, Cabezas M, Salgado G, Sabin LL, Hamer DH.

BACKGROUND:
Studies of zinc as an adjunct to treatment of severe pneumonia in children have shown mixed results, possibly because of poor information on zinc status and respiratory pathogens.

OBJECTIVE:
We evaluated the effect of zinc given with standard antimicrobial treatment on the duration of respiratory signs in children with severe pneumonia. Zinc status and pathogens were assessed.

DESIGN:
Children aged 2-59 mo with severe pneumonia who were admitted to the main children's hospital in Quito, Ecuador, were given standard antibiotics and randomly allocated to receive zinc supplements twice daily or a placebo. Measurements included anthropometric variables, breastfeeding, hemoglobin, plasma zinc, and common bacteria/viral respiratory pathogens. The primary outcome was time to resolution of respiratory signs. The secondary outcome was treatment failure.

RESULTS:
We enrolled 225 children in each group. There was no difference between groups in time to resolution of respiratory signs or treatment failure; pathogens were not associated with outcomes. Tachypnea and hypoxemia resolved faster in older children (P = 0.0001) than in younger ones. Higher basal zinc concentration (P = 0.011) and better height-for-age z score (HAZ) (P = 0.044) were associated with faster resolution of chest indrawing. Better weight-for-height z score (WHZ) (P = 0.031) and HAZ (P = 0.048) were associated with faster resolution of tachypnea. Increased C-reactive protein was associated with a longer duration of tachypnea (P = 0.044).

CONCLUSIONS:
Zinc did not affect time to pneumonia resolution or treatment failure, nor did type of respiratory pathogens affect outcomes. **Higher basal zinc and better HAZ and WHZ were associated with reduced time to resolution of respiratory signs**. These results suggest the need for prevention of chronic zinc deficiency and improvement of general nutritional status among Ecuadorian children.

J Trop Pediatr. 2014 Apr;60(2):104-11. doi: 10.1093/tropej/fmt089. Epub 2013 Nov 5.

Effect of zinc supplementation on duration of hospitalization in Tanzanian children presenting with acute pneumonia.

Fataki MR, Kisenge RR, Sudfeld CR, Aboud S, Okuma J, Mehta S, Spiegelman D, Fawzi WW.

BACKGROUND:

Zinc supplementation prevents incident pneumonia in children; however, the effect for pneumonia treatment remains unclear.

METHODS: A randomized, double-blind, placebo-controlled trial of zinc supplements (daily 25 mg) adjunct to antibiotic treatment of radiology-confirmed acute pneumonia was conducted among hospitalized children (6-36 months) in Dar es Salaam, Tanzania.

RESULTS: The trial was stopped early due to low enrollment, primarily owing to exclusion of children outside the age range and >3 days of prior illness. Among children enrolled (n = 94), zinc supplementation indicated no beneficial effect on the duration of hospitalization (IRR: 0.69; 95% CI 0.45-1.06; p = 0.09) or the proportion of children who were hospitalized for <3 days (RR: 0.85; 95% CI: 0.57-1.25; p = 0.40) or <5 days (RR: 1.01; 95% CI: 0.83-1.23; p = 0.92) (IRRs and RRs >1.0 favor zinc).

CONCLUSIONS: Although underpowered, this randomized trial provided no evidence for a beneficial effect of zinc supplementation adjunct to antibiotics for hospitalized children.

Vitamin D and pneumonia

ISRN Pediatr. 2013 Dec 19;2013:459160. eCollection 2013.

Vitamin D Supplementation for the Treatment of Acute Childhood Pneumonia: A Systematic Review.

Das RR, Singh M, Panigrahi I, Naik SS.

BACKGROUND:
Studies have found an increased incidence of vitamin D deficiency in children with pneumonia; however, there is no conclusive data regarding the direct effect of vitamin D supplementation in acute pneumonia.

METHODS:
A comprehensive search was performed of the major electronic databases till September 2013. Randomized controlled trials (RCTs) comparing treatment with vitamin D3 versus placebo in children ≤5 years old with pneumonia were included.

RESULTS:
Out of 32 full text articles, 2 RCTs including 653 children were eligible for inclusion. One trial used a single 100,000 unit of oral vitamin D3 at the onset of pneumonia. **There was no significant difference in the mean (±SD) number of days to recovery between the vitamin D3 and placebo arms (*P* = 0.17).** Another trial used oral vitamin D3 (1000 IU for <1 year and 2000 IU for >1 year) for 5 days in children with severe pneumonia. Median duration of resolution of severe pneumonia was similar in the two groups (intervention, 72 hours; placebo, 64 hours). Duration of hospitalization and time to resolution of tachypnea, chest retractions, and inability to feed were also comparable between the two groups.

CONCLUSIONS:
Oral vitamin D supplementation does not help children under-five with acute pneumonia.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24455293/

Influenza

Lancet Infect Dis. 2014 Feb;14(2):109-18. doi: 10.1016/S1473-3099(13)70267-6. Epub 2013 Nov 22.

Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial.

Fry AM, Goswami D, Nahar K, Sharmin AT, Rahman M, Gubareva L, Azim T, Bresee J, Luby SP, Brooks WA.

BACKGROUND: Influenza causes substantial morbidity and mortality worldwide. Few data exist for the efficacy of neuraminidase inhibitors, which are the only readily available influenza treatment options, especially in low-income settings. **We assessed the efficacy of treatment with the neuraminidase inhibitor oseltamivir to reduce patient illness and viral shedding in people with influenza**, in whom treatment was started within 5 days of symptom onset, in an urban setting in Bangladesh.

METHODS: We undertook a double-blind, randomised, controlled trial between May, 2008, and December, 2010. Patients with a positive rapid influenza test identified by surveillance of households in Kamalapur, Bangladesh were randomly allocated on a 1:1 basis to receive oseltamivir or placebo twice daily for 5 days. Randomisation lists for individuals enrolled less than 48 h and 48 h or longer since illness onset were generated with permuted blocks of variable length between two and eight. Participants and study staff were masked to treatment group. Participants provided nasal wash specimens at enrolment and 2, 4, and 7 days later, and were visited daily to record symptoms. All specimens were tested for influenza with reverse-transcriptase PCR, and if the result was positive, we isolated the virus. **The primary endpoints were duration of clinical illness and viral shedding in patients treated less than and more than 48 h since illness onset** and the frequency of oseltamivir resistance during treatment. Analyses were intention to treat unless otherwise specified. This trial is registered with ClinicalTrials.gov, number NCT00707941.

FINDINGS: Overall, 1190 people with a median age of 5 years (IQR 2-9) were enrolled: 794 (67%) less than 48 h since symptom onset and 396 (33%) 48 h or longer since symptom onset. **592 participants were assigned to placebo and 598 to oseltamivir**. **The median duration of symptoms was shorter in the oseltamivir group (3 days, IQR 1-5) than in the placebo group (4 days, 1-6; p=0.01).** When stratified by timing of treatment initiation, in participants enrolled 48 h or longer since illness onset, the median duration of symptoms was similar in both groups (oseltamivir 3 days [IQR 2-5], placebo 3 days [1-5]; p=0.04). **The median duration of symptoms was reduced by 1 day in the group given oseltamivir who were enrolled less than 48 h since symptom onset compared with those given placebo**, but this difference was

not significant. **In those with all swab specimens (n=1134), oseltamivir significantly reduced virus isolation on days 2 (placebo 374 [66%] vs oseltamivir 321 [56%]; difference 15.2%, 95% CI 9.5-20.8, p=0.0004), 4 (241 [43%] vs 174 [30%]; difference 30.2%, 95% CI 24.6-35.8, p<0.0001), and 7 (68 [12%] vs 36 [6%]; difference 47.5%, 95% CI 44.2-50.8, p=0.0009).** In participants enrolled 48 h or longer since illness onset, oseltamivir treatment significantly reduced virus isolation on days 2 and 4, but not day 7. In participants enrolled less than 48 h since illness onset, oseltamivir treatment significantly reduced virus isolation on days 2, 4, and 7. The emergency of resistance to oseltamivir during treatment was rare overall (<1%) and in influenza A H1N1pdm09 viruses (3.9%).

INTERPRETATION: Oseltamivir treatment resulted in a modest reduction in the duration of symptoms and virus shedding in people with uncomplicated influenza infections, even when treatment was started 48 h or longer after illness onset.

Oxygen and CPAP

J Trop Pediatr. 2014 Feb;60(1):33-9. doi: 10.1093/tropej/fmt074. Epub 2013 Aug 25.

Aftermath of a clinical trial: evaluating the sustainability of a medical device intervention in Ghana.

Wilson PT, Brooks JC, Otupiri E, Moresky RT, Morris MC.

A randomized controlled trial recently demonstrated that continuous positive airway pressure (CPAP) effectively decreases respiratory rate in children presenting to Ghanaian district hospitals with respiratory distress. A follow-up study 16 months later evaluated the extent to which the skills and equipment necessary for CPAP use have been maintained. Seven of eight CPAP machines were functional, but five of eight oxygen concentrators and three of four electric generators were non-functional. Nurses trained by US study personnel (first-generation) and nurses trained by Ghanaian nurses after the study (second-generation) were evaluated on CPAP knowledge and skills. Twenty-eight nurses participated in the study, 9 first-generation and 19 second-generation. First-generation trainees scored significantly higher than second-generation trainees on both skills and knowledge assessments (p = 0.003). Appropriate technical support and training must be ensured to address equipment maintenance. Protocolization of the training program, in conjunction with skills and knowledge assessment, may improve acquisition and retention among second- and future-generation trainees.

Bronchiolitis

Indian Pediatr. 2013 Aug;50(8):743-7. Epub 2012 Dec 5.

Hypertonic (3%) saline vs 0.93% saline nebulization for acute viral bronchiolitis: a randomized controlled trial.

Sharma BS, Gupta MK, Rafik SP.

OBJECTIVE: To compare the length of hospital stay (primary) and improvement in clinical severity scores (secondary) among children with bronchiolitis nebulized with 3 % hypertonic saline or 0.9% saline.

DESIGN: Randomized double blind controlled trial.

SETTINGS: Tertiary care teaching hospital.

PATIENTS: Hospitalized children (1-24 months) with acute bronchiolitis of moderate severity.

INTERVENTION: Nebulization of 4 ml of 3% hypertonic saline or 4 mL of 0.9% saline, along with 2.5 mg salbutamol, at 4-hourly intervals till the patient was ready for discharge.

RESULTS: Baseline characteristics were similar in two groups. Median clinical severity score at admission was 6 (IQR-1) in both the groups. **Clinical severity scores monitored afterwards 12-hourly till discharge (132 h) did not show statistically significant differences in 3% and 0.9% saline groups.** Mean length of hospital stay (time to reach predefined clinical severity score<3) was 63.93 ± 22.43 h in 3% saline group and 63.51 ± 21.27 h in 0.9% saline group (P=0.878). No adverse events were reported by the parents, caregivers or treating medical attendants in both groups.

CONCLUSION: Nebulized 3 % saline is not superior to 0.9% saline in infants with clinically diagnosed acute bronchiolitis.

http://www.indianpediatrics.net/aug2013/743.pdf

Simple cough

Paediatr Int Child Health. 2013 Aug;33(3):145-50. doi: 10.1179/2046905513Y.0000000064.

A randomized controlled trial of chelated zinc for prevention of the common cold in Thai school children.

Rerksuppaphol S, Rerksuppaphol L.

BACKGROUND: The common cold is responsible for the largest proportion of school and work absenteeism and is a huge economic burden. None of the currently available interventions is clearly effective for prevention or treatment.

OBJECTIVE: To assess the efficacy of 15-mg chelated zinc (zinc bis-glycinate) given once a day for 3 months during the winter season to healthy school children aged 8-13 years to prevent symptoms of the common cold.

METHODS: In a double-blind randomized controlled trial, zinc bis-glycinate 15 mg or matching placebo once a day for 3 months was administered to healthy school children aged 8-13 years. Primary outcomes were any symptom of cold (fever, cough, rhinorrhoea) during the

study period, and secondary outcomes were vomiting, diarrhoea, use of antibiotics, school absence for any reason, school absence because of a cold and duration of all symptoms.

RESULTS: Of 50 children in each group, 42 (84%) in the zinc group and 41 (82%) in the placebo group (P = 1.00) developed at least one symptom of a cold. There was no difference in the incidence of fever, cough, rhinorrhoea, school absence and school absence related to the common cold compared with children in the placebo group. However, duration of cough [median (IQR) 1.0 (0.0-6.0) vs 6.0 (0.0-13.3) days], rhinorrhoea [median (IQR) 2.0 (0.0-7.0) vs 5.5 (1.0-15.3) days] and the frequency of having two or more symptoms of the common cold [median (IQR) 0.0 (0.0-1.0) vs 1.0 (0.0-5.3) days] were reduced significantly in the intervention group (P<0.01).

CONCLUSIONS: **Zinc bis-glycinate given in a dose of 15 mg once a day for 3 months failed to reduce the incidence of the common cold in 8 to 13-year-old school children, but decreased the number of days on which children suffered from cough, rhinorrhoea and the likelihood of having two or more symptoms of the common cold**.

http://www.maneyonline.com/doi/abs/10.1179/2046905513Y.0000000064?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Indian J Pediatr. 2013 Nov;80(11):891-5. doi: 10.1007/s12098-013-1002-2. Epub 2013 Apr 17.

To compare the effect of dextromethorphan, promethazine and placebo on nocturnal cough in children aged 1-12 y with upper respiratory infections: a randomized controlled trial.

Bhattacharya M, Joshi N, Yadav S.

OBJECTIVES: To evaluate whether promethazine and dextromethorphan reduce nocturnal cough and improve sleep quality in children aged 1-12 y with upper respiratory tract infection (URI).

METHODS: This randomised double-blinded placebo-controlled trial was conducted in Pediatric outpatient department of Lok Nayak Hospital, Delhi. After randomization into promethazine, dextromethorphan and placebo groups, parental assessment of 120 children with URI for nocturnal cough severity (child), post-tussive vomiting (child) and sleep quality (child and parent) on the night before enrolment and after 3 d of assigned medication was measured using an internally validated indigenously prepared ordinal scale.

RESULTS: Entire cohort improved in all the study parameters after 3 d. However, no superior benefit was noted when individual parameters were compared in the promethazine and dextromethorphan groups with the placebo group. Adverse effects were more frequent in the dextromethorphan and promethazine groups although the difference was not statistically significant.

CONCLUSIONS: **Nocturnal cough in URI is self-resolving and dextromethorphan and promethazine prescribed for the same are not superior to placebo.**

Adolescent health

(See also Vaccines - HPV vaccine)

J Int AIDS Soc. 2014 Mar 19;17:18585. doi: 10.7448/IAS.17.1.18585. eCollection 2014.

Early adolescent pregnancy increases risk of incident HIV infection in the Eastern Cape, South Africa: a longitudinal study.

Christofides NJ, Jewkes RK, Dunkle KL, Nduna M, Shai NJ, Sterk C.

INTRODUCTION: Adolescents having unprotected heterosexual intercourse are at risk of HIV infection and unwanted pregnancy. However, there is little evidence to indicate whether pregnancy in early adolescence increases the risk of subsequent HIV infection. In this paper, we tested the hypothesis that adolescent pregnancy (aged 15 or younger) increases the risk of incident HIV infection in young South African women.

METHODS: We assessed 1099 HIV-negative women, aged 15-26 years, who were volunteer participants in a cluster-randomized, controlled HIV prevention trial in the predominantly rural Eastern Cape province of South Africa. All of these young women had at least one additional HIV test over two years of follow-up. Outcomes were HIV incidence rates per 100 person years and HIV incidence rate ratios (IRRs) estimated by Poisson multivariate models. Three pregnancy categories were created for the Poisson model: early adolescent pregnancy (a first pregnancy at age 15 years or younger); later adolescent pregnancy (a first pregnancy at age 16 to 19 years); and women who did not report an adolescent pregnancy. Models were adjusted for study design, age, education, time since first sexual experience, socio-economic status, childhood trauma and herpes simplex virus type 2 infection.

RESULTS: HIV incidence rates were 6.0 per 100 person years over two years of follow-up. **The adjusted IRR was 3.02 (95% CI 1.50-6.09) for a pregnancy occurring at age 15 or younger.** Women with pregnancies occurring between 16 and 19 years of age did not have a higher incidence of HIV (IRR 1.08; 95% CI 0.64-1.84). Early adolescent pregnancies were associated with higher partner numbers and a greater age difference with partners.

CONCLUSIONS: **Early adolescent pregnancies increase the incidence of HIV among South African women.** The higher risk is associated with sexual risk behaviours such as higher partner numbers and a greater age difference with partners rather than a biological explanation of hormonal changes during pregnancy.

J Adolesc Health. 2013 Nov;53(5):602-8. doi: 10.1016/j.jadohealth.2013.01.014. Epub 2013 Apr 6.

Let's Talk!, A South African worksite-based HIV prevention parenting program.

Bogart LM, Skinner D, Thurston IB, Toefy Y, Klein DJ, Hu CH, Schuster MA.

PURPOSE: South African adolescents have high HIV risk, yet few prevention interventions are effective. Parents play a pivotal role in youths' healthy sexual development and may be at risk themselves. We tested whether Let's Talk!, a worksite-based parenting program, improves

parent-child communication about HIV and sexual health and parent condom use self-efficacy and behavior.

METHODS: We culturally adapted Let's Talk! in two languages, drawing on formative research and community stakeholder input. We then conducted a small randomized test at a large public worksite in Cape Town, South Africa. The intervention consisted of 5 weekly 2-hour group sessions for parents of youth aged 11-15. Sixty-six parents (64% female) and their 64 adolescents (41% female) completed surveys before and 1-2 weeks post-intervention; surveys assessed comfort with talking about sex, communication about 16 HIV- and sex-related topics, and parents' condom use self-efficacy and behavior. Thirty-four black African (Xhosa language) and 32 coloured (mixed-race; Afrikaans language) parent-child dyads participated. Parents were randomized to intervention (n = 34) and control (n = 32) groups; randomization was stratified by language.

RESULTS: Multivariate regressions indicated that the intervention significantly increased parents' comfort with talking to their adolescent about sex, b(SE) = .98(.39), p = .02, and the number of sex- and HIV-related topics discussed with their adolescent, b(SE) = 3.26(1.12), p = .005. Compared with control parents, intervention parents were more likely to discuss new sex- and HIV-related topics not discussed before the intervention, b(SE) = 2.85(.80), p <.001. The intervention significantly increased parents' self-efficacy for condom use, b(SE) = .60(.21), p = .007.

CONCLUSIONS: Let's Talk! holds promise for improving parent-child communication, a critical first step in preventing HIV among youth.

http://linkinghub.elsevier.com/retrieve/pii/S1054-139X(13)00056-6

AIDS Behav. 2014 Feb;18(2):381-9. doi: 10.1007/s10461-013-0439-7.

Reported physical and sexual abuse in childhood and adult HIV risk behaviour in three African countries: findings from Project Accept (HPTN-043).

Richter L, Komárek A, Desmond C, Celentano D, Morin S, Sweat M, Chariyalertsak S, Chingono A, Gray G, Mbwambo J, Coates T.

Childhood sexual and physical abuse have been linked to adolescent and adult risky sexual behaviors, including early sexual debut, an increased number of sexual partners, unprotected sex, alcohol and drug use during sex and sexual violence. This paper explores these relationships among both men and women who report histories of childhood abuse from representative samples of communities in three countries in southern and eastern Africa (South Africa, Zimbabwe and Tanzania). Data were collected as part of a 3-year randomized community trial to rapidly increase knowledge of HIV status and to promote community responses through mobilisation, mobile testing, provision of same-day HIV test results and post-test support for HIV. The results indicate that reported childhood sexual and physical abuse is high in all three settings, also among men, and shows strong relationships with a range of sexual risk behaviors, including age at first sex (OR -0.6 (CI: -0.9, -0.4, p < 0.003)-among men, OR -0.7 (CI: -0.9, -0.5, p < 0.001)-among women), alcohol (OR 1.43 (CI: 1.22, 1.68, p < 0.001)-men, OR 1.83 (CI: 1.50, 2.24, p < 0.001)-women) and drug use (OR 1.65 (CI: 1.38, 1.97, p < 0.001)-

men, OR 3.14 (CI: 1.95, 5.05, p < 0.001)-women) and two forms of partner violence-recent forced sex (OR 2.22 (CI: 1.66, 2.95, p < 0.001)-men, OR 2.76 (CI: 2.09, 3.64, p < 0.001)-women) and ever being hurt by a partner (OR 3.88 (CI: 2.84, 5.29, p < 0.001)-men, OR 3.06 (CI: 2.48, 3.76, p < 0.001)-women). **Individuals abused in childhood comprise between 6 and 29 % of young adult men and women living in these African settings and constitute a population at high risk of HIV infection**.

http://dx.doi.org/10.1007/s10461-013-0439-7

J Child Psychol Psychiatry. 2013 Nov;54(11):1231-41. doi: 10.1111/jcpp.12094. Epub 2013 Jun 6.

Group trauma-focused cognitive-behavioural therapy with former child soldiers and other war-affected boys in the DR Congo: a randomised controlled trial.

McMullen J, O'Callaghan P, Shannon C, Black A, Eakin J.

BACKGROUND: The Democratic Republic of Congo (DRC) has been home to the world's deadliest conflict since World War II and is reported to have the largest number of child soldiers in the world. Despite evidence of the debilitating impact of war, no group-based mental health or psychosocial intervention has been evaluated in a randomised controlled trial for psychologically distressed former child soldiers.

METHOD: A randomised controlled trial involving 50 boys, aged 13-17, including former child soldiers (n = 39) and other war-affected boys (n = 11). They were randomly assigned to an intervention group, or wait-list control group. The intervention group received a 15-session, group-based, culturally adapted **Trauma-Focused Cognitive-Behavioural Therapy (TF-CBT)** intervention. Assessment interviews were completed at baseline, postintervention and 3-month follow-up (intervention group).

RESULTS: Analysis of Covariance (ANCOVA) demonstrated that, in comparison to the wait-list control group, **the TF-CBT intervention group had highly significant reductions in posttraumatic stress symptoms, overall psychosocial distress, depression or anxiety-like symptoms, conduct problems and a significant increase in prosocial behaviour** (p < .001 for all). Effect sizes were higher when former child soldier scores were separated for sub-analysis. Three-month follow-up of the intervention group found that treatment gains were maintained.

CONCLUSIONS: **A culturally modified, group-based TF-CBT intervention was effective in reducing posttraumatic stress and psychosocial distress in former child soldiers and other war-affected boys.**

http://onlinelibrary.wiley.com/resolve/openurl?genre=article&sid=nlm:pubmed&issn=0021-9630&date=2013&volume=54&issue=11&spage=1231

J Health Commun. 2013;18(11):1384-96. doi: 10.1080/10810730.2013.778371. Epub 2013 Oct 4.

The impact of Thai family matters on parent-adolescent sexual risk communication attitudes and behaviors.

Cupp PK, Atwood KA, Byrnes HF, Miller BA, Fongkaew W, Chamratrithirong A, Rhucharoenpornpanich O, Rosati MJ, Chookhare W.

This article reports on a combined family-based substance abuse and HIV-prevention intervention targeting families with 13-14-year-old children in Bangkok, Thailand. Families (n = 340) were randomly and proportionally selected from 7 districts in Bangkok with half randomly assigned to an experimental or control condition. **Families in the intervention condition were exposed to 5 interactive booklets about adolescent substance use and risky sexual behavior.** Trained health educators followed up by phone to encourage completion of each booklet. Primary outcomes reported in this article include whether the intervention increased the frequency of parent-child communication in general or about sexual risk taking in particular as well as whether the intervention reduced discomfort discussing sexual issues. The authors also tested to see whether booklet completion was associated with communication outcomes at the 6-month follow-up. Multivariate findings indicate that the intervention had a significant impact on the frequency of general parent-child communication on the basis of child reports. The intervention had a marginal impact on the frequency of parent-child communication about sexual issues on the basis of parent reports. Booklet completion was associated with reduced discomfort discussing sex and was marginally associated with frequency of parent-child discussion of sex on the basis of parent reports only. These findings indicate that a family-based program can influence communication patterns.

http://www.tandfonline.com/doi/abs/10.1080/10810730.2013.778371?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Allergy

J Allergy Clin Immunol Pract. 2014 Mar-Apr;2(2):179-85. doi: 10.1016/j.jaip.2013.09.019. Epub 2014 Jan 1.

Long-term, randomized safety study of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) in subjects with chronic rhinitis.

Berger WE, Shah S, Lieberman P, Hadley J, Price D, Munzel U, Bhatia S.

BACKGROUND: MP29-02 is a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate (FP) in an advanced delivery system for the treatment of seasonal allergic rhinitis.

OBJECTIVE: The objective of this study was to evaluate the long-term safety of MP29-02 in subjects with chronic allergic (perennial) or nonallergic (vasomotor) rhinitis.

METHODS: This was a 1-year, randomized, open-label, active-controlled, parallel-group study in subjects with chronic allergic or nonallergic rhinitis. A total of 612 subjects were randomized in a 2:1 ratio to (1) MP29-02, one spray per nostril twice daily (total daily doses of azelastine hydrochloride and FP were 548 mcg and 200 mcg, respectively); or (2) FP, 2 sprays per nostril once daily (total daily dose 200 mcg). Safety and tolerability assessments were made at months 1, 3, 6, 9, and 12.

RESULTS: The incidence of treatment-related adverse events was low with both MP29-02 (9.4%) and FP (11.1%), with no evidence of late-occurring adverse events. Nasal examinations showed no evidence of nasal mucosal ulcerations or septal perforations with MP29-02, and the overall incidence of adverse findings was reduced as the study progressed. There were no unusual or unexpected ocular examination findings and no clinically important laboratory findings or clinically important differences between groups in fasting AM serum cortisol levels after 12 months of treatment.

CONCLUSIONS: MP29-02 was well tolerated. There were no safety findings that would preclude the long-term use of MP29-02 in the treatment of allergic rhinitis.

Am J Rhinol Allergy. 2013 Jul-Aug;27(4):299-303. doi: 10.2500/ajra.2013.27.3923.

Randomized double-blind placebo-controlled crossover study of efficacy of pollen blocker cream for perennial allergic rhinitis.

Li Y, Wang D, Liu Q, Liu J.

BACKGROUND: This study evaluates the efficacy and safety of a pollen blocker cream in treatment of perennial allergic rhinitis (PAR) in a Chinese population.

METHODS: A randomized double-blind placebo-controlled, crossover trial was conducted in the Outpatient Department of the Eye, Ear, Nose, and Throat Hospital, Fudan University, Shanghai, China. Patients diagnosed with PAR were randomly assigned to receive pollen blocker cream or placebo, which was applied and evenly distributed to the lower internal nose region three times daily for a total of 30 days. The primary outcome measures for efficacy were nasal symptom scores (NSSs) and quality of life scores (QoLSs). Medication scores and adverse events were also monitored.

RESULTS:
After application of pollen blocker, the mean NSS fell from 23.1 to 12.4 points, and the QoLSs fell from 83.9 to 53.2 points ($p < 0.001$). The decrease in NSSs of pollen blocker (10.7) was highly significant compared with the placebo (3.6; $p < 0.001$). The decrease in QoLSs of pollen blocker was 30.7 compared with 7.1 in the placebo group, and the difference was also significant ($p < 0.05$). Interestingly, the mean NSS of the placebo group also decreased from 23.7 to 20.1 ($p < 0.05$). Additionally, the efficacy of pollen blocker was superior to the placebo both in adults and in children. However, there was no significant difference for individual symptoms of rhinorrhea, nasal itching, sneezing, and nasal congestion between the pollen blocker group and placebo group ($p > 0.05$). Only one mild epistaxis was reported.

CONCLUSION: The pollen blocker was significantly more effective than the placebo in relieving allergy symptoms and improving life quality of PAR in 30 Chinese people.

http://openurl.ingenta.com/content/nlm?genre=article&issn=1945-8924&volume=27&issue=4&spage=299&aulast=Li

Anaemia and iron deficiency

JAMA. 2013 Sep 4;310(9):938-47. doi: 10.1001/jama.2013.277129.

Effect of iron fortification on malaria incidence in infants and young children in Ghana: a randomized trial.

Zlotkin S, Newton S, Aimone AM, Azindow I, Amenga-Etego S, Tchum K, Mahama E, Thorpe KE, Owusu-Agyei S.

IMPORTANCE: In sub-Saharan Africa, malaria is a leading cause of childhood morbidity and iron deficiency is among the most prevalent nutritional deficiencies. In 2006, the World Health Organization and the United Nations Children's Fund released a joint statement that recommended limiting use of iron supplements (tablets or liquids) among children in malaria-endemic areas because of concern about increased malaria risk. As a result, anemia control programs were either not initiated or stopped in these areas.

OBJECTIVE: To determine the effect of providing a micronutrient powder (MNP) with or without iron on the incidence of malaria among children living in a high malaria-burden area.

DESIGN, SETTING, AND PARTICIPANTS: Double-blind, cluster randomized trial of children aged 6 to 35 months (n = 1958 living in 1552 clusters) conducted over 6 months in 2010 in a rural community setting in central Ghana, West Africa. A cluster was defined as a compound including 1 or more households. Children were excluded if iron supplement use occurred within the past 6 months, they had severe anemia (hemoglobin level <7 g/dL), or severe wasting (weight-for-length z score <-3).

INTERVENTIONS: **Children were randomized by cluster to receive a MNP with iron (iron group; 12.5 mg/d of iron) or without iron (no iron group).** The MNP with and without iron were added to semiliquid home-prepared foods daily for 5 months followed by 1-month of further monitoring. Insecticide-treated bed nets were provided at enrollment, as well as malaria treatment when indicated.

MAIN OUTCOMES AND MEASURES:
Malaria episodes in the iron group compared with the no iron group during the 5-month intervention period.

RESULTS: **In intention-to-treat analyses, malaria incidence overall was significantly lower in the iron group compared with the no iron group (76.1 and 86.1 episodes/100 child-years, respectively; risk ratio (RR), 0.87 [95% CI, 0.79-0.97]), and during the intervention period (79.4 and 90.7 episodes/100 child-years, respectively; RR, 0.87 [95%**

CI, 0.78-0.96]). In secondary analyses, these differences were no longer statistically significant after adjusting for baseline iron deficiency and anemia status overall (adjusted RR, 0.87; 95% CI, 0.75-1.01) and during the intervention period (adjusted RR, 0.86; 95% CI, 0.74-1.00).

CONCLUSION AND RELEVANCE: In a malaria-endemic setting in which insecticide-treated bed nets were provided and appropriate malaria treatment was available, daily use of a MNP with iron did not result in an increased incidence of malaria among young children.

http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2013.277129

Comment

This is an interesting result, different from a previous large trial from 2006 in Zanzibar which found that routine iron supplementation as associated with increased rates of hospitalisation, morbidity and all-cause deaths and deaths due to malaria in a malaria endemic community (Sazawal S, *Lancet*. 2006;367(9505):133-143). WHO now recommends:

- In settings where the prevalence of anaemia in preschool (24–59 months) or school-age (5–12 years) children is 20% or higher, WHO recommends the intermittent use of iron supplements as a public health intervention to improve iron status and reduce the risk of anaemia among children.
- In malaria-endemic areas, the provision of iron supplements should be implemented in conjunction with measures to prevent, diagnose and treat malaria.

http://www.who.int/elena/titles/iron_infants_malaria/en/

J Trop Pediatr. 2014 Feb;60(1):40-6. doi: 10.1093/tropej/fmt071. Epub 2013 Aug 20.

Assessment of drinking water fortification with iron plus ascorbic Acid or ascorbic Acid alone in daycare centers as a strategy to control iron-deficiency anemia and iron deficiency: a randomized blind clinical study.

de Almeida CA, De Mello ED, Ramos AP, João CA, João CR, Dutra-de-Oliveira JE.

OBJECTIVE: Assess drinking water fortification with iron and/or ascorbic acid as a strategy to control iron-deficiency anemia and iron deficiency.

METHODS: Randomized blind clinical study, **fortifying drinking water to 153 pre-school children during 3 months, with iron and ascorbic acid (A), ascorbic acid (B) or plain water (C).** Hemoglobin (Hb), mean corpuscular volume (MCV) and ferritin were measured.

RESULTS: Within the groups, Hb raised in all three groups, MCV in A and B and ferritin in A. The difference between time points 0 and 1 was significant between A and B for Hb, when A and B were compared with C for MCV and when A was compared with either B or C for ferritin.

CONCLUSIONS: **Water fortification is efficient in controlling iron deficiency and anemia.** Iron stores' recovery depends on a more effective offer of iron. Water fortification must be preceded by a careful assessment of the previous nutritional status.

Anaesthesia and intensive care

(See also Treatment of severe malaria)

Intensive Care Med. 2014 Jun 18. [Epub ahead of print]

Dexamethasone pretreatment for 24 h versus 6 h for prevention of postextubation airway obstruction in children: a randomized double-blind trial.

Baranwal AK, Meena JP, Singhi SC, Muralidharan J.

PURPOSE: Multidose steroid pretreatment is effective in preventing postextubation airway obstruction (PEAO) in adults, however controversy continues for children. This study was designed as a randomized, placebo-controlled, double-blind trial to compare the effect of 24-h pretreatment with dexamethasone (24hPD) versus 6-h pretreatment (6hPD) on PEAO and reintubation in children at a tertiary care hospital in a developing economy.

METHODS: Hundred twenty-four children (3 months to 12 years) intubated for ≥48 h and planned to have extubation during next 24 h were randomized to receive 24hPD (0.5 mg/kg/dose, q6h, total of six doses; n = 66) or 6hPD (total of three doses; n = 58). Patients with preexistent upper airway conditions, chronic respiratory diseases, steroid therapy in last 7 days, gastrointestinal bleeding, hypertension, and hyperglycemia and those likely to have poor airway reflexes were excluded.

RESULTS: The two groups were similar at baseline. 24hPD reduced the incidence of PEAO (43/66 versus 48/58; p = 0.027) with absolute risk reduction of 17 %. It also reduced the incidence of reintubation, though nonsignificantly, by half [5/61 versus 9/58; relative risk (RR), 1.09; 95 % confidence interval (CI), 0.96-1.25]. Time to recovery from PEAO among non-reintubated patients was shorter among 24hPD patients (p = 0.016). No adverse event was noted with dexamethasone use. Intubation duration >7 days and cuffed tracheal tubes were found to be independent risk factors for PEAO (odds ratio 6 and 3.12, respectively).

CONCLUSIONS: 24-h pretreatment with multidose dexamethasone reduced the incidence of PEAO and the time to recover from it. 24hPD should be considered for high-risk children intubated for >48 h in the study setting. Further studies with larger sample size from different socioeconomic background are desirable to validate these findings.

J Anesth. 2014 Feb;28(1):12-8. doi: 10.1007/s00540-013-1657-x. Epub 2013 Jun 26.

Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: a double-blind, randomized, placebo-controlled trial.

Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK.

INTRODUCTION: Providing anesthesia to children undergoing MRI is challenging. Adequate premedication, administered noninvasively, would make the process smoother. In this study, we compare the efficacy of intranasal dexmedetomidine (DXM) with the intranasal administration of ketamine for procedural sedation in children undergoing MRI.

METHODS: We studied 150 children, between 1 and 10 years of age, divided randomly into three groups (DXM, K, and S). For blinding, every child received the intranasal drugs twice; syringe S1, 60 min before, and syringe S2, 30 min before intravenous (IV) cannulation. For children in group DXM, S1 contained DXM (1 μg/kg) and S2 was plain saline. Children in group K received saline in S1 and ketamine (5 mg/kg) in S2 whereas children in group S received saline in both S1 and S2. The child's response to drug administration, ease of IV cannulation, the satisfaction of the anesthesiologist and child's parents with the premedication, and the total propofol dose required for the satisfactory conduct of the procedure were compared. We also compared the time to awakening and discharge of the child as well as the occurrence of any side effects with these drugs.

RESULTS: **Both DXM and ketamine were equally effective as premedication in these patients.** Most of the children accepted the intranasal drugs with minimal discomfort; 90.4 % of the anesthesiologists in the DXM group and 82.7 % in the ketamine group were satisfied with the conditions for IV cannulation whereas only 21.3 % were satisfied in the saline group. The total dose of propofol used was less in the study groups. Furthermore, children in group DXM and group K had earlier awakening and discharge than those in group S.

CONCLUSION: DXM and ketamine were equally effective, by the intranasal route, as premedication in children undergoing MRI.

http://dx.doi.org/10.1007/s00540-013-1657-x

Indian Pediatr. 2014 Feb;51(2):113-8. Epub 2013 Sep 5.

Intranasal clonidine vs. midazolam as premedication in children: a randomized controlled trial.

Mitra S, Kazal S, Anand LK.

OBJECTIVE: To compare anxiolysis produced by intranasal clonidine with intranasal midazolam as premedication in children undergoing surgery.

DESIGN: Double-blind randomized controlled study.

SETTING: Tertiary-care hospital, July 2009 to June 2010.

PATIENTS: 60 American Society of Anesthesiologists physical status I-II surgical patients aged 1-10 yr.

INTERVENTION: Participants randomly allocated to receive either intranasal clonidine 4 mcg/kg (Group I) with atropine or intranasal midazolam 0.3 mg/kg (Group II).

OUTCOME MEASURES: Primary: satisfactory anxiolysis at 30 min after drug administration. Secondary: satisfactory mask acceptance, times of onset of sedation and anxiolysis, drug acceptance, level of sedation, wake-up score and side effects.

RESULTS: All children achieved satisfactory anxiolysis at 30 min. Group I fared significantly better than GroupII on mask acceptance (100% in Group I vs. 80% in Group II; P=0.024), drug acceptance (93% vs. 13%; P<0.001) and proportion of patients with satisfactory wake up scores (100% vs. 53%; P<0.001). Group II patients had significantly faster onset of sedation (median 10 min vs. 15 min; P<0.05) but not that of anxiolysis compared to Group-I (median 10 min for both groups; P>0.05). Side effects were significantly more frequent in Group II.

CONCLUSIONS: Though intranasal midazolam produced faster sedation, both the drugs produced satisfactory anxiolysis at 30 min.

http://www.indianpediatrics.net/feb2014/113.pdf

J Neurosurg Anesthesiol. 2013 Jul;25(3):271-8. doi: 10.1097/ANA.0b013e31828cb6c0.

Effect of intraoperative dexmedetomidine on postoperative recovery profile of children undergoing surgery for spinal dysraphism.

Gupta N, Rath GP, Prabhakar H, Dash HH.

BACKGROUND: Smooth recovery from anesthesia is desirable in children undergoing surgery for spinal dysraphism who are nursed in prone position during the postoperative period. Dexmedetomidine may be beneficial in these children owing to its sedative, anxiolytic, and opioid-sparing properties with minimal respiratory depression.

METHODS: Thirty-six children with spinal dysraphism at lumbosacral area, aged 8 to 12 years, undergoing corrective surgery were randomized to receive either dexmedetomidine or volume-matched saline (placebo) after positioned prone until beginning of skin closure. Inspired concentration of sevoflurane was changed to keep the bispectral index score between 45 and 55. Perioperative hemodynamics, intraoperative fentanyl and sevoflurane consumption, and postoperative recovery profile and fentanyl consumption was observed by blinded observers. Postoperative pain, emergence agitation (EA), and discharge readiness from postanesthesia care unit was evaluated using the modified objective pain score, agitation Cole score, and modified Aldrete score, respectively. Fentanyl 0.5-1 μg/kg was administered for pain (objective pain score ≥4) or severe EA (agitation Cole score ≥4) lasting for >5 minutes.

RESULTS: The 2 groups did not differ significantly with respect to demographics, duration of anesthesia, emergence, and extubation times. The intraoperative consumption of sevoflurane and fentanyl was significantly less in dexmedetomidine group (0.2±0.1 vs. 0.3±0.1 mL/min, P<0.0001 and 2.3±0.5 vs. 3.1±0.6 μg/kg, P=0.0001, respectively), along with a lower mean heart rate (P<0.001). The mean systolic blood pressure (P=0.98) and incidence of bradycardia and hypotension was comparable in between the 2 groups. Postoperatively, the children in dexmedetomidine group had significantly lower pain scores (P<0.0001), agitation scores (P<0.0001), and time to achieve full modified Aldrete score [0 (0 to 10) vs. 10 (0 to 20) min,

P=0.001]. The postoperative consumption of fentanyl was significantly less in dexmedetomidine group [0 (0 to 1.04) vs. 0.88 (0 to 3) µg/kg, P=0.003], along with a longer time of first analgesic requirement [600 (5 to 2100) vs. 5 (5 to 185) min, P=0.0001]. The mean heart rate and systolic blood pressure were higher in placebo group (P<0.001), whereas no difference was observed in respiratory rate (P=0.73) and arterial oxygen saturation (P=0.36). The number of patients with postoperative nausea and vomiting was significantly lower in dexmedetomidine group [2 (11.1%) vs. 9 (50%), P=0.03].

CONCLUSIONS: **Intraoperative use of dexmedetomidine in children undergoing spinal surgery results in a favorable recovery profile with reduced postoperative pain and EA, without adverse perioperative hemodynamic effects.**

Anesth Analg. 2013 Dec;117(6):1401-7. doi: 10.1213/ANE.0b013e3182a8ee52.

The effectiveness of pudendal nerve block versus caudal block anesthesia for hypospadias in children.

Naja ZM, Ziade FM, Kamel R, El-Kayali S, Daoud N, El-Rajab MA.

BACKGROUND: Caudal block (CB) has some disadvantages, one of which is its short duration of action after a single injection. For hypospadias repair, pudendal nerve block (PNB) might be a suitable alternative since it has been successfully used for analgesia for circumcision. We evaluated PNB compared with CB as measured by total analgesic consumption 24 hours postoperatively.

METHODS: In this prospective, double-blinded study, patients were randomized into 2 groups, either receiving CB or nerve stimulator-guided PNB. **In the PNB group, patients were injected with 0.3 mL/kg 0.25% bupivacaine and 1 µg/kg clonidine.** In the CB group, patients were injected with 1 mL/kg 0.25% bupivacaine and 1 µg/kg clonidine. Analgesic consumption was assessed during the first 24 hours postoperatively. The "objective pain scale" developed by Hannalah and Broadman was used to assess postoperative pain.

RESULTS: Eighty patients participated in the study, 40 in each group. The mean age in the PNB group was 3.1 (1.1) years and in the CB group was 3.2 (1.1) years. The mean weights in the PNB and CB groups were 15.3 (2.8) kg and 15.3 (2.2) kg, respectively. The percentage of patients who received analgesics during the first 24 hours were significantly higher in the CB (70%) compared with the PNB group (20%, P < 0.0001). The average amount of analgesics consumed per patient within 24 hours postoperatively was higher in the CB group (paracetamol P < 0.0001, Tramal P =0.003).

CONCLUSION: Patients who received PNB had reduced analgesic consumption and pain within the first 24 hours postoperatively compared with CB.

http://meta.wkhealth.com/pt/pt-core/template-journal/lwwgateway/media/landingpage.htm?issn=0003-2999&volume=117&issue=6&spage=1401

*** Crit Care Med. 2014 Apr 1. [Epub ahead of print]

Randomized Controlled Trial Comparing Cerebral Perfusion Pressure-Targeted Therapy Versus Intracranial Pressure-Targeted Therapy for Raised Intracranial Pressure due to Acute CNS Infections in Children.

Kumar R, Singhi S, Singhi P, Jayashree M, Bansal A, Bhatti A.

OBJECTIVE: In children with acute CNS infection, management of raised intracranial pressure improves mortality and neuromorbidity. We compared cerebral perfusion pressure-targeted approach with the conventional intracranial pressure-targeted approach to treat raised intracranial pressure in these children.

DESIGN: Prospective open-label randomized controlled trial.

SETTING: PICU in a tertiary care academic institute.

PATIENTS: Hundred ten children (1-12 yr) with acute CNS infections having raised intracranial pressure and a modified Glasgow Coma Scale score less than or equal to 8 were enrolled.

INTERVENTIONS: Patients were randomized to receive either cerebral perfusion pressure-targeted therapy (n = 55) (maintaining cerebral perfusion pressure ≥ 60 mm Hg, using normal saline bolus and vasoactive therapy-dopamine, and if needed noradrenaline) or intracranial pressure-targeted therapy (n = 55) (maintaining intracranial pressure < 20 mm Hg using osmotherapy while ensuring normal blood pressure). The primary outcome was mortality up to 90 days after discharge from PICU. Secondary outcome was modified Glasgow Coma Scale score at 72 hours after enrollment, length of PICU stay, duration of mechanical ventilation, and hearing deficit and functional neurodisability at discharge and 90-day follow-up.

MEASUREMENTS AND MAIN RESULTS:
A 90-day mortality in intracranial pressure group (38.2%) was significantly higher than cerebral perfusion pressure group (18.2%; relative risk = 2.1; 95% CI, 1.09-4.04; p = 0.020). The cerebral perfusion pressure group in comparison with intracranial pressure group had significantly higher median (interquartile range) modified Glasgow Coma Scale score at 72 hours (10 [8-11] vs 7 [4-9], p < 0.001), shorter length of PICU stay (13 d [10.8-15.2 d] vs 18 d [14.5-21.5 d], p = 0.002) and mechanical ventilation (7.5 d [5.4-9.6 d] vs 11.5 d [9.5-13.5 d], p = 0.003), lower prevalence of hearing deficit (8.9% vs 37.1%; relative risk = 0.69; 95% CI, 0.53-0.90; p = 0.005), and neurodisability at discharge from PICU (53.3% vs 82.9%; relative risk = 0.37; 95% CI, 0.17-0.81; p = 0.005) and 90 days after discharge (37.8% vs 70.6%; relative risk = 0.47; 95% CI, 0.27-0.83; p = 0.004).

CONCLUSION:
Cerebral perfusion pressure-targeted therapy, which relied on more frequent use of vasopressors and lesser use of hyperventilation and osmotherapy, was superior to intracranial pressure-targeted therapy for management of raised intracranial pressure in children with acute CNS infection in reducing mortality and morbidity.

*** Crit Care Med. 2013 Jul;41(7):1754-60. doi: 10.1097/CCM.0b013e31828a2a85.

Milrinone therapy for enterovirus 71-induced pulmonary edema and/or neurogenic shock in children: a randomized controlled trial.

Chi CY, Khanh TH, Thoa le PK, Tseng FC, Wang SM, Thinh le Q, Lin CC, Wu HC, Wang JR, Hung NT, Thuong TC, Chang CM, Su IJ, Liu CC.

OBJECTIVE: Enterovirus 71-induced brainstem encephalitis with pulmonary edema and/or neurogenic shock (stage 3B) is associated with rapid mortality in children. In a small pilot study, we found that milrinone reduced early mortality compared with historical controls. This prospective, randomized control trial was designed to provide more definitive evidence of the ability of milrinone to reduce the 1-week mortality of stage 3B enterovirus 71 infections.

DESIGN: Prospective, unicenter, open-label, randomized, controlled study.

SETTING: Inpatient ward of a large tertiary teaching hospital in Ho Chi Minh City, Vietnam.

PATIENTS: Children (≤ 18 yr old) admitted with proven enterovirus 71-induced pulmonary edema and/or neurogenic shock.

INTERVENTIONS: Patients were randomly assigned to receive intravenous milrinone (0.5 μg/kg/min) (n = 22) or conventional management (n = 19). Both groups received dopamine or dobutamine and intravenous immunoglobulin.

MEASUREMENTS AND MAIN RESULTS:
The primary endpoint was 1-week mortality. The secondary endpoints included length of ventilator dependence and hospital stay and adverse events. The median age was 2 years with a predominance of boys in both groups. **The 1-week mortality was significantly lower, 18.2% (4/22) in the milrinone compared with 57.9% (11/19) in the conventional management group (relative risk = 0.314 [95% CI, 0.12-0.83], p = 0.01).** The median duration of ventilator-free days was longer in the milrinone treatment group (p = 0.01). There was no apparent neurologic sequela in the survivors in either group, and no drug-related adverse events were documented.

CONCLUSIONS: Milrinone significantly reduced the 1-week mortality of enterovirus 71-induced pulmonary edema and/or neurogenic shock without adverse effects. Further studies are needed to determine whether milrinone might be useful to prevent progression of earlier stages of brainstem encephalitis.

Comment

Milrinone is an inhibitor of cyclic nucleotide phosphodiesterase III that is used to treat low cardiac output. Brainstem encephalitis is associated with acute pulmonary oedema. In this study there was significantly lower early mortality among children with brainstem encephalitis who received milrinone as part of their treatment, compared to those who did not. The study was very small, and milrinone was used in the context of other high quality intensive care treatment and monitoring. The study did not report mortality at the time of hospital discharge, and no echocardiographic findings are reported. Funding for the study is not stated in the paper. Other milrinone trials have been industry sponsored, but this may not have been.

Asthma and chronic lung disease

Indian J Pediatr. 2014 Jul;81(7):655-9. doi: 10.1007/s12098-013-1334-y. Epub 2014 Feb 21.

Montelukast versus Budesonide as a First Line Preventive Therapy in Mild Persistent Asthma in 2 to 18 y.

Shah MB, Gohil J, Khapekar S, Dave J.

OBJECTIVES: To compare the efficacy of oral Montelukast and inhaled Budesonide as a first line preventive therapy in mild persistent asthma in age group 2-18 y.

METHODS: This prospective randomized controlled clinical study was conducted for 12 wk. Sixty patients of mild persistent asthma aged 2 to 18 y were randomly allocated to either oral Montelukast (n = 60) or inhaled Budesonide (n = 60) group. Outcomes measured were improvement in peak expiratory flow rate (PEFR), forced expiratory volume 1 s/forced vital capacity (FEV1/FVC), day time and night time symptoms and frequency of exacerbations and need to change medications.

RESULTS: There was significant improvement in PEFR, FEV1/FVC, day time and night time symptoms and frequency of exacerbations in both groups. However, more significant improvement in FEV1/FVC (CI 95 %, p = 0.029) and day time symptoms (CI 95 %, p = 0.002) was seen in Budesonide group compared to Montelukast group.

CONCLUSIONS: The present study suggests that oral Montelukast is not inferior to Budesonide in treatment of mild persistent asthma in 2 to 18 y children in terms of control of symptoms and improvement in pulmonary function tests over a 12 wk period. However, there was more significant improvement in day time symptoms, more significant increase in FEV1/FVC ratio and less exacerbation in patients receiving Budesonide compared to those receiving Montelukast. However, side effects due to long term use of steroids such as growth stunting and bone osteopenia should also be considered before recommending. Trial registered at CTRI no. REF/2012/09/004035.

Thorax. 2014 Apr;69(4):312-9. doi: 10.1136/thoraxjnl-2013-203600. Epub 2013 Nov 19.

Once-daily fluticasone furoate (FF)/vilanterol reduces risk of severe exacerbations in asthma versus FF alone.

Bateman ED, O'Byrne PM, Busse WW, Lötvall J, Bleecker ER, Andersen L, Jacques L, Frith L, Lim J, Woodcock A.

BACKGROUND: Combination therapy with an inhaled corticosteroid (ICS) and long-acting β2 agonist (LABA) is recommended for patients with asthma symptomatic on ICS alone. However, there is ongoing debate regarding the risk-benefit ratio of using LABA in asthma.

OBJECTIVE: To evaluate the effect of the addition of a novel LABA, vilanterol (VI), to a once-daily ICS, fluticasone furoate (FF), on the risk of severe asthma exacerbations in patients with uncontrolled asthma.

METHODS: This randomised double-blind comparative study of variable duration (≥ 24-78 weeks) was designed to finish after 330 events (each patient's first on-treatment severe asthma exacerbation). 2019 patients with asthma aged ≥ 12 years with ≥ 1 recorded exacerbation within 1 year were randomised and received FF/VI 100/25 µg or FF 100 µg, administered once daily in the evening. The primary endpoint was time to first severe exacerbation; secondary endpoints were rate of severe asthma exacerbations per patient per year and change in trough evening forced expiratory volume in 1 s (FEV1) from baseline.

RESULTS: **Compared with FF, FF/VI delayed the time to first severe exacerbation (HR 0.795, 95% CI 0.642 to 0.985) and reduced the annualised rate of severe exacerbations (rate reduction 25%, 95% CI 5% to 40%).** Significantly greater improvements in trough FEV1 ($p<0.001$) were observed with FF/VI than with FF at weeks 12, 36, 52 and at endpoint. Both treatments were well tolerated with similar rates of treatment-related adverse events and on-treatment serious adverse events.

CONCLUSIONS: Once-daily FF/VI reduced the risk of severe asthma exacerbations and improved lung function compared with FF alone, with good tolerability and safety profile in adolescents and adults with asthma currently receiving ICS.

http://thorax.bmj.com/cgi/pmidlookup?view=long&pmid=24253831

Altern Ther Health Med. 2014 Mar-Apr;20(2):18-23.

Is yoga training beneficial for exercise-induced bronchoconstriction?

Tahan F, Eke Gungor H, Bicici E.

BACKGROUND: Some studies have shown the beneficial effects of yoga for individuals with bronchial hyperreactivity with regard to (1) a reduction in the use of rescue medication, (2) an increase in exercise capacity, and (3) an improvement in lung function. Despite the fact that yoga is promising as a new treatment for pediatric patients, further studies are needed to assess the use of this training for asthma management.

OBJECTIVE: This study was performed to assess the beneficial effects of yoga in exercise-induced bronchoconstriction (EIB) in children.

DESIGN: The study was prospective, with no control group. Participants were randomly chosen among the new patients at the unit.

SETTING: This study was conducted in the Erciyes University School of Medicine, Pediatric Allergy Unit, in Kayseri, Turkey.

PARTICIPANTS: Two groups of asthmatic children aged 6-17 y were enrolled in the study: (1) children with positive responses to an exercise challenge (n = 10), and (2) those with negative responses (n = 10).

INTERVENTION: Both groups attended 1-h sessions of yoga training 2 ×/wk for 3 mo.

OUTCOME MEASURES: Researchers administered spirometric measurement to all children before and immediately after participating in an exercise challenge. This process was performed at baseline and at the study's end. Age, gender, IgE levels, eosinophil numbers, and spirometric measurement parameters including forced expiratory volume in 1 sec (FEV1), forced expiratory flow 25%-75% (FEF25%-75%), forced vital capacity (FVC), peak expiratory flow percentage (PEF%), and peak expiratory flow rate (PEFR) were compared using the Mann-Whitney U test and the Wilcoxon test. A P value < .05 was considered significant.

RESULTS: At baseline, no significant differences were observed between the groups regarding demographics or pre-exercise spirometric measurements (P > .05, Mann-Whitney U test). Likewise, no significant differences in spirometric measurements existed between the groups regarding the change in responses to an exercise challenge after yoga training (P > .05, Wilcoxon test). For the exercise-response-positive group, the research team observed a significant improvement in maximum forced expiratory volume 1% (FEV1%) fall following the exercise challenge after yoga training (P > .05, Wilcoxon test). All exercise-response-positive asthmatics became exerciseresponse-negative asthmatics after yoga training.

CONCLUSION: This study showed that training children in the practice of yoga had beneficial effects on EIB. It is the research team's opinion that yoga training can supplement drug therapy to achieve better control of asthma.

Cardiovascular health

Int J Cardiol. 2013 Sep 30;168(2):888-91. doi: 10.1016/j.ijcard.2012.10.090. Epub 2012 Dec 13.

Echocardiographic screening for rheumatic heart disease: age matters.

Kane A, Mirabel M, Touré K, Périer MC, Fazaa S, Tafflet M, Karam N, Zourak I, Diagne D, Mbaye A, Kane M, Diack B, Jouven X, Marijon E.

BACKGROUND: Echocardiography is emerging as a screening tool for rheumatic heart disease (RHD) in endemic regions. The vast majority of surveys have been limited to children. We sought to appreciate the interest of including adolescents in their late teens in such school screening programmes.

METHODS: School-based echocardiography cross-sectional survey conducted in Dakar, Senegal (March 2010). A total of 2004 school attendees were randomly selected and enrolled in the study, among which 1116 were aged 5-15 years old (group 1), and 888 were 16-18 years old (group 2). Case detection rates and phenotype of RHD were compared according to age groups.

RESULTS: A total of 22 youngsters were suspected by on-site echocardiography, 12 in group 1 and 10 in group 2. Among the 12 RHD cases suspected on-site in group 1, 6 (50%) were eventually considered as confirmed RHD, compared to 9 out of 10 (90%) in group 2,

giving prevalence rates of 5.4 (CI 95% 2.0-11.7) and 10.1 (CI 95% 4.6-19.2) per 1000 in group 1 and group 2, respectively. The proportion of marked/advanced lesions was 33% in group 1, and 89% in group 2 (p=0.08). Mean concordance rates between the 3 reviewers were 40% for group 1, compared to 93% in group 2 (p=0.05).

CONCLUSIONS: **Extension of screening to adolescents in their late teens should be considered with interest in the light of the higher prevalence of the disease and relative clarity of subclinical cardiac lesions that could be more easily detected in the field.**

Eur J Pediatr. 2013 Aug;172(8):1097-103. doi: 10.1007/s00431-013-2012-9. Epub 2013 May 1.

Risk factors for high blood pressure in low income children aged 3-4 years.

Vitolo MR, da Costa Louzada ML, Rauber F, Campagnolo PD.

This study aimed to evaluate the effect of dietary sodium intake on blood pressure among low income children aged 3-4 years. Data were collected during a randomized trial conducted in São Leopoldo, Brazil, with 500 mother-child pairs recruited from the maternity ward of a local hospital. Breastfeeding data were obtained during the children's first year of life. At 3 to 4 years of age, children's anthropometric, dietary, and blood pressure assessments were obtained. Sodium intake was estimated from two multiple-pass 24-h dietary recalls. Systolic blood pressure > 90th percentile for age, sex, and height was classified as high systolic blood pressure, according to the population-based percentiles provided by the Task Force on Hypertension Control in Children and Adolescents. Blood pressure data were obtained from 331 children at 3 to 4 years. The mean value of systolic blood pressure was 91.31 mmHg (SD = 8.30 mmHg) and 5.2% (n = 17) presented high systolic blood pressure. The results of the multivariable analyses showed that children who consumed more than 1,200 mg of sodium/day and with waist-to-height ratio higher than 0.5 presented, respectively, 3.32 (95%CI 0.98-11.22) and 8.81 (95%CI 2.13-36.31) greater risk of having high systolic blood pressure. Exclusive breastfeeding, child overweight and change in body mass index z score during the first year of life were not associated with the outcome. Conclusions: The results of this study suggest that at preschool age sodium intake and high waist-to-height ratio are risk factors for high systolic blood pressure.

Int J Food Sci Nutr. 2013 Sep;64(6):687-93. doi: 10.3109/09637486.2013.775224. Epub 2013 Mar 12.

The effects of synbiotic supplementation on some cardio-metabolic risk factors in overweight and obese children: a randomized triple-masked controlled trial.

Safavi M, Farajian S, Kelishadi R, Mirlohi M, Hashemipour M.

[1]Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran.

Recent studies have suggested some beneficial effects of probiotics on controlling excess weight in adults; such experience is limited in the pediatric age group. This study aimed to assess the anti-obesity and lipid-lowering effects of a synbiotic supplement among children and adolescents. We conducted a randomized triple-masked controlled trial among 70 participants aged 6-18 years with body mass index (BMI) equal or higher than 85th percentile. They were randomly assigned to two groups of equal number to receive synbiotic or placebo for 8 weeks. At the end of the trial, decrease in BMI Z-score, waist circumference, and waist-to-hip ratio were significantly higher in the synbiotic group than in the placebo group. Likewise, synbiotic group had significant decrease in serum triglycerides, total- and low density lipoprotein-cholesterol levels. The beneficial effects of a synbiotic supplement on controlling excess weight and some cardio-metabolic risk factors among children and adolescents can be considered in clinical practice.

Vasc Health Risk Manag. 2013;9:703-9. doi: 10.2147/VHRM.S52187. Epub 2013 Nov 11.

Lipid profiles and inflammatory markers after periodontal treatment in children with congenital heart disease and at risk for atherosclerosis.

Bresolin AC[1], Pronsatti MM, Pasqualotto LN, Nassar PO, Jorge AS, da Silva EA, Nassar CA.

Due to the biological associations between periodontal and cardiovascular diseases, as well as the fact that atherosclerosis begins in childhood, behavior based on oral health care and metabolic control from an early age is essential for patients with cardiovascular disease. **The aim of this research was to examine the effect of full-mouth scaling and root planing on the reduction of periodontal disease in children with congenital heart disease.** In this study, treatments were related to clinical periodontal parameters and also to blood ones, such as lipid profile and inflammatory markers. The patients were divided into two groups: group 1 (n=17), scaling and root planing; and group 2 (n=16), full-mouth scaling and root planing. The results showed a significant improvement in clinical periodontal parameters ($P<0.05$) in both groups. Considering lipid parameters, total cholesterol, triglycerides, and very-low-density lipoprotein parameters showed significant improvement ($P<0.05$). There was also an improvement in C-reactive protein (ultrasensitive) in the group treated with scaling and root planing ($P<0.05$). Fibrinogen and interleukin-6 parameters improved ($P<0.05$) in both groups. We suggest that both periodontal treatments were effective in children with congenital heart disease, though neither demonstrated superiority.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24250224/

Indian J Psychol Med. 2014 Apr;36(2):158-63. doi: 10.4103/0253-7176.130982.

A Placebo Controlled Trial on Add-on Modafinil on the Anti-psychotic Treatment Emergent Hyperglycemia and Hyperlipidemia.

Prasuna PL, Vijay Sagar KJ, Sudhakar TP, Rao GP.

Modafinil is non stimulant drug which is marketed for mainly Narcolepsy and daytime drowsiness. The clinical experience and Summary of Product Characteristics (SPC) of the drug also mentions Anorexia as one of the side effects. Anorexia can have a direct impact on the

carbohydrate and fat intake, which may, in turn, regulate antipsychotic induced dyslipidemia and Hyperglycaemia.

AIM: To compare the effects of Modafinil- ADDON with Placebo add on with olanzapine, Clozapine and Risperidone in drug naive subjects and people who were started on the drugs within 15days of assessment.

MATERIALS AND METHODS: Randomized, Double blind, Placebo controlled study, which was conducted at two centres, one at department of Psychiatry, S.V Medical College, Tirupati and the other at Asha hospitals, Hyderabad. Seventy two patient were randomised, sixty three patients have completed the total study period of three months. The dose of Modafinil was 200 mgs constantly as Flexible doses of Olanzapine, Clozapine and Risperidone as per clinical need was given. A baseline, three week and twelve week assessments of Fasting blood Glucose and fasting Serum cholesterol were made and the groups were compared on these parameters.

RESULTS: From baseline to week 3 there was a significant raise in Fasting serum cholesterol followed by a fall from week 3 to week 12 in the Modafinil addon group, though it could not be considered a drug for hypercholesteremia like Statins in controlling hyperlipidaemia. The implications of these findings were discussed.

Community and primary health services

(see also Environmental health)

World Dev. 2014 Feb;54(100):325-337.

Involving Communities in the Targeting of Cash Transfer Programs for Vulnerable Children: Opportunities and Challenges.

Robertson L, Mushati P, Skovdal M, Eaton JW, Makoni JC, Crea T, Mavise G, Dumba L, Schumacher C, Sherr L, Nyamukapa C, Gregson S.

We used baseline data, collected in July-September 2009, from a randomized controlled trial of a cash transfer program for vulnerable children in eastern Zimbabwe to investigate the effectiveness, coverage, and efficiency of census- and community-based targeting methods for reaching vulnerable children. Focus group discussions and in-depth interviews with beneficiaries and other stakeholders were used to explore community perspectives on targeting. Community members reported that their participation improved ownership and reduced conflict and jealousy. However, all the methods failed to target a large proportion of vulnerable children and there was poor agreement between the community- and census-based methods.

Am J Public Health. 2013 Dec;103(12):2131-5. doi: 10.2105/AJPH.2013.301459.

The challenge of promoting interventions to prevent disease in impoverished populations in rural western Kenya.

Schilling K, Person B, Faith SH, Otieno R, Quick R.

Poverty is a critical social determinant of health. A particular approach toward mitigating inequitable access to health services in Kenya has been through a community-based distribution program implemented by the Safe Water and AIDS Project (SWAP) that has achieved modest uptake of public health interventions. To explore reasons for modest uptake, we asked program participants about child health problems, daily tasks, household expenditures, and services needed by their communities. Respondents identified child health problems consistent with health data and reported daily tasks, expenses, and needed services that were more related to basic needs of life other than health. These findings highlight the challenges of implementing potentially self-sustaining preventive interventions at scale in poor populations in the developing world.

Dengue

(see Vaccines - dengue)

Development and mental health

(See also Maternal mental health, Anaemia and iron deficiency, Micronutrients and food

Soc Sci Med. 2013 Nov;97:250-8. doi: 10.1016/j.socscimed.2013.06.020. Epub 2013 Jun 26.

Effectiveness of a parenting program in Bangladesh to address early childhood health, growth and development.

Aboud FE, Singla DR, Nahil MI, Borisova I.

A stratified cluster design was used to evaluate a 10-month parenting program delivered to mothers of children in rural Bangladesh. **Intervention mothers through a combination of group meetings and home visits received messages along with an illustrative card concerning hygiene, responsive feeding, play, communication, gentle discipline, and nutritious foods. Control mothers received the standard government care**. Three months prior, 463 children between 4 and 14 months in a subdistrict of western Bangladesh were administered the cognitive, receptive language and expressive language Bayley III subtests, their length was taken and past week illness recorded. Gross motor milestones were reported by the mother and verified through observation. Mothers were interviewed concerning their practices: preventive health practices, dietary diversity, home stimulation, and knowledge about development milestones. Maternal depressive symptoms were assessed as a measure of emotional availability. Family sociodemographic variables included maternal education, family assets, decision-making and mobility autonomy. One month after the end of the program, mothers and their children were again assessed. Comparisons were made between intervention and control children who were under-12 months vs. 12 months and older at the start of the program. This may be a critical age, when children begin to be upright and mobile enough to explore on their own and be less dependent on parenting stimulation. **Analyses yielded strong intervention effects on the three Bayley subtests and on parenting practices related to stimulation and knowledge of development milestones.** Age effects were found only for dietary diversity in that younger children in the program benefited more than older ones. However, all children became more stunted. Findings are discussed in terms of theories of behaviour change and parenting, critical ages for parenting programs, and implications for program delivery.

J Child Psychol Psychiatry. 2014 May 9. doi: 10.1111/jcpp.12247. [Epub ahead of print]

Development of children at risk for adverse outcomes participating in early intervention in developing countries: a randomized controlled trial.

Wallander JL, Bann CM, Biasini FJ, Goudar SS, Pasha O, Chomba E, McClure E, Carlo WA.

BACKGROUND: Previous research has indicated positive effects of **early developmental intervention (EDI)** on the development of children in developing countries. Few studies, however, have examined longitudinally when differential treatment effects may be observed and whether differential outcomes are associated with exposure to different risk factors and country of implementation. Also, birth asphyxia as a risk condition has not been well studied. To address these limitations, we conducted a randomized controlled trial to test the hypothesis that there will be differential developmental trajectories favoring those who receive EDI versus a health education intervention in children in rural areas of India, Pakistan, and Zambia.

METHODS: **Children with and without birth asphyxia were randomized to EDI or control intervention**, which was implemented by parents who received training in biweekly home visits initiated before child age 1 month and continuing until 36 months. Development was assessed in 376 children at ages 12, 24, and 36 months using the Bayley Scales of Infant Development and Ages & Stages Questionnaire administered by evaluators blind to intervention assignment and risk condition.

RESULTS: Longitudinal mixed model analysis indicated that EDI resulted in better development over 36 months in cognitive abilities, regardless of risk condition, maternal resources, child gender, or country. Psychomotor development and parent-reported general development showed similar trends as for cognitive abilities, but were not statistically different between intervention conditions. Developmental differences were observed first at 36 months of age.

CONCLUSION: **Early developmental intervention has promise for improving development in children across developing countries when exposed to various risk conditions**. EDI should be one prominent approach used to begin to address long-term outcomes and intergenerational transmission of poverty.

Comment

Interesting to see the research being done in the last few years on improving development in high risk children. Impressive work coming from several countries in South Asia, and especially Bangladesh as illustrated by the first paper in this section

Brain Dev. 2013 Oct;35(9):870-6. doi: 10.1016/j.braindev.2012.11.001. Epub 2012 Dec 11.

Efficacy of modified constraint induced movement therapy in improving upper limb function in children with hemiplegic cerebral palsy: a randomized controlled trial.

Choudhary A, Gulati S, Kabra M, Singh UP, Sankhyan N, Pandey RM, Kalra V.

METHODS: Thirty-one children were randomly assigned to receive the mCIMT (N=16) with conventional therapy or conventional therapy alone (N=15). Children were evaluated three times (at enrollment, follow up at 4 weeks and 12 weeks). The primary outcome measure was difference in "change in mean total QUEST scores" at 4 weeks of intervention between the intervention and the control arm.

RESULTS: After 4 weeks of intervention, mCIMT group showed significant change in the affected upper limb in QUEST scores (10.7 ± 5.2 vs 1.4 ± 1.7, $p<0.001$) and time (s) to complete nine-hole-pegboard test compared with control group [60(0-130) vs 5(-12 to 30), $p<0.001$]. The improvement observed in upper limb function after 4 weeks of intervention persisted 8 weeks after discontinuation of intervention in mCIMT group.

CONCLUSION: The modified constraint induced movement therapy appears to be effective in improving upper limb function in 3-8 years old hemiplegic cerebral palsy children.

Comment
Constraint Induced Movement Therapy (CIMT) involves the combination of restraint of the unaffected limb and intensive use of the affected limb. Types of restraints include a sling or triangular bandage, a splint, or a hand splint. It has been used in the rehabilitation after strokes, and for the management of cerebral palsy.

Brain Dev. 2013 Aug;35(7):647-53. doi: 10.1016/j.braindev.2012.10.012. Epub 2012 Nov 17.

Comparative assessment of therapeutic response to physiotherapy with or without botulinum toxin injection using diffusion tensor tractography and clinical scores in term diplegic cerebral palsy children.

Chaturvedi SK, Rai Y, Chourasia A, Goel P, Paliwal VK, Garg RK, Rathore RK, Pandey CM, Gupta RK.

The present study was to compare the effects of combined therapy [botulinum (BTX) plus physiotherapy] with physiotherapy alone using diffusion tensor imaging (DTI) derived fractional anisotropy (FA) values of motor and sensory fiber bundles and clinical grade of the disability to see the value of BTX in term children with spastic diplegic cerebral palsy (CP). Clinically diagnosed 36 children participated in the study. All these children were born at term, and had no history of seizures. **The study was randomly categorized into two groups: group I (n=18) - physiotherapy alone and group II (n=18) - physiotherapy plus BTX injection.** Quantitative diffusion tensor tractography on all these children was performed on motor and sensory fiber bundles on baseline as well as after 6months of therapy. Motor function and clinical grades were also measured by gross motor function measures (GMFM) scale on both occasions. We observed significant change in FA value in motor and sensory fiber bundle as well as in GMFM scores at 6months compared to baseline study in both the groups. However, delta change and relative delta change in FA values of sensory and motor fiber bundle as well as GMFM score between group I and group II was statistically insignificant. **We conclude that addition of BTX to physiotherapy regimen does not influence the outcome at 6months with similar insult in children with term diplegic spastic CP.** This information may influence management of diplegic CP especially in developing countries, where BTX is beyond the reach of these children.

Clin Rehabil. 2013 Aug;27(8):686-96. doi: 10.1177/0269215513476721. Epub 2013 Mar 15.

A comparison of treadmill training and overground walking in ambulant children with cerebral palsy: randomized controlled clinical trial.

Grecco LA, Zanon N, Sampaio LM, Oliveira CS.

DESIGN: Randomized controlled clinical trial.

SETTING: Physical therapy clinics.

SUBJECTS: Thirty-six children with cerebral palsy (levels I-III of the Gross Motor Functional Classification System) randomly divided into two intervention groups.

INTERVENTIONS: Experimental group (17 children) submitted to treadmill training without partial weight support. Overground walking group (18 children) submitted to gait training on a fixed surface (ground). Training was performed for seven consecutive weeks (two sessions per week), with four subsequent weeks of follow-up.

RESULTS: Both groups demonstrated improvements on the 6-minute walk test (experimental group from 227.4 SD 49.4 to 377.2 SD 93.0; overground walking group from 222.6 SD 42.6 to 268.0 SD 45.0), timed up-and-go test (experimental group from 14.3 SD 2.9 to 7.8 SD 2.2; overground walking group from 12.8 SD 2.2 to 10.5 SD 2.5), Pediatric Evaluation Disability Inventory (experimental group from 128.0 SD 19.9 to 139.0 SD 18.4; overground walking group from 120.8 SD 19.0 to 125.8 SD 12.2), Gross Motor Function Measure-88 (experimental group from 81.6 SD 8.7 to 93.0 SD 5.7; overground walking group from 77.3 SD 7.0 to 80.8 SD 7.2), Berg Balance Scale (experimental group from 34.9 SD 8.5 to 46.7 SD 7.6; overground walking group from 31.9 SD 7.0 to 35.7 SD 6.8) after treatment. The experimental group demonstrated greater improvements than the overground walking group both after treatment and during follow up ($p < 0.05$).

CONCLUSION: **Treadmill training proved more effective than training with overground walking regarding functional mobility, functional performance, gross motor function and functional balance in children with cerebral palsy.**

Early Hum Dev. 2013 Sep;89(9):667-74. doi: 10.1016/j.earlhumdev.2013.04.013. Epub 2013 May 28.

Developmental effects of micronutrient supplementation and malaria in Zanzibari children.

Olney DK, Kariger PK, Stoltzfus RJ, Khalfan SS, Ali NS, Tielsch JM, Sazawal S, Black R, Allen LH, Pollitt E.

BACKGROUND: Children's development is affected by the interplay of internal and external factors and changes in one factor can precipitate changes in multiple developmental domains.

AIMS: The aim of this study was to test a theoretical model of children's development using structural equation modeling.

STUDY DESIGN: This was designed as a substudy of a randomized, placebo-controlled, 2 × 2 factorial trial of the effects of daily supplementation with iron (12.5 mg) + folic acid (50 μg) (FeFA) with or without zinc (10 mg) (Zn) on child mortality.

SUBJECTS: Zanzibari children aged 5-9 mo (n = 106) and 10-14 mo (n = 141) at baseline were included in this sub study.

OUTCOME MEASURES: Longitudinal data on children's hemoglobin, growth, malaria infection, motor development, motor activity, and language development and caregiver behavior were used to test the fit of the **theoretical model** for two age groups and to examine the direct and indirect relationships among the variables in the model.

RESULTS: The theoretical models were a good fit to the data for both age groups and revealed that **FeFA with or without Zn had positive effects on motor development**. FeFA alone had negative effects on language development in both age groups and Zn alone had negative effects on language development in children aged 10-14 mo. The incidence of malaria had negative effects on the majority of health and development outcomes in children aged 5-9 mo, and on motor development and hemoglobin in children aged 10-14 mo.

CONCLUSIONS: These findings illustrate how nutrition and health factors can affect different domains of development and how these changes can precipitate changes in other domains. More work is needed to better understand the multiple impacts of internal and external factors on children's development and how changes in developmental domains interact with each other over time to determine children's overall developmental trajectory. The randomized, placebo-controlled study was registered as an International Standard Randomized Controlled Trial, number ISRCTN59549825.

Comment
It is unclear why iron and folic acid would have a negative impact on language development. Previous trials have shown that iron supplementation has positive effects on cognitive development and school performance. The trial raises more questions than it answers, but was just modelling, rather than true observed effects within a clinical trial.

Int J Pediatr Otorhinolaryngol. 2013 Sep;77(9):1545-50. doi: 10.1016/j.ijporl.2013.06.031. Epub 2013 Jul 27.

Comparing the effect of auditory-only and auditory-visual modes in two groups of Persian children using cochlear implants: a randomized clinical trial.

Oryadi Zanjani MM, Hasanzadeh S, Rahgozar M, Shemshadi H, Purdy SC, Mahmudi Bakhtiari B, Vahab M.

OBJECTIVE: Since the introduction of cochlear implantation, researchers have considered children's communication and educational success before and after implantation. Therefore, the present study aimed to compare auditory, speech, and language development scores following

one-sided cochlear implantation between two groups of prelingual deaf children educated through either auditory-only (unisensory) or auditory-visual (bisensory) modes.

DESIGN: A randomized controlled trial with a single-factor experimental design was used.

METHODS: The study was conducted in the Instruction and Rehabilitation Private Centre of Hearing Impaired Children and their Family, called Soroosh in Shiraz, Iran. We assessed 30 Persian deaf children for eligibility and 22 children qualified to enter the study. They were aged between 27 and 66 months old and had been implanted between the ages of 15 and 63 months. **The sample of 22 children was randomly assigned to two groups: auditory-only mode and auditory-visual mode; 11 participants in each group were analyzed. In both groups, the development of auditory perception, receptive language, expressive language, speech, and speech intelligibility was assessed pre- and post-intervention by means of instruments which were validated and standardized in the Persian population.**

RESULTS: No significant differences were found between the two groups. **The children with cochlear implants who had been instructed using either the auditory-only or auditory-visual modes acquired auditory, receptive language, expressive language, and speech skills at the same rate.**

CONCLUSION: Overall, spoken language significantly developed in both the unisensory group and the bisensory group. Thus, both the auditory-only mode and the auditory-visual mode were effective. Therefore, it is not essential to limit access to the visual modality and to rely solely on the auditory modality when instructing hearing, language, and speech in children with cochlear implants who are exposed to spoken language both at home and at school when communicating with their parents and educators prior to and after implantation. The trial has been registered at IRCT.ir, number IRCT201109267637N1.

Child Adolesc Psychiatry Ment Health. 2013 Nov 7;7(1):37. doi: 10.1186/1753-2000-7-37.

Effect of yoga or physical exercise on physical, cognitive and emotional measures in children: a randomized controlled trial.

Telles S, Singh N, Bhardwaj AK, Kumar A, Balkrishna A.

BACKGROUND: Previous studies have separately reported the effects of physical exercise and yoga in children, showing physical, cognitive and emotional benefits.

OBJECTIVES: The present randomized controlled trial assessed the effects of yoga or physical exercise on physical fitness, cognitive performance, self-esteem, and teacher-rated behavior and performance, in school children.

METHODS: 98 school children between 8 to 13 years were randomized as yoga and physical exercise groups {n = 49 each; (yoga: 15 girls, group mean age 10.4 ± 1.2 years), (physical exercise: 23 girls, group mean age 10.5 ± 1.3 years)}. Both groups were blind assessed after allocation, using: (i) the Eurofit physical fitness test battery, (ii) Stroop color-word task for children, (iii) Battle's self-esteem inventory and (iv) the teachers' rating of the children's obedience, academic performance, attention, punctuality, and behavior with friends and teachers. After assessments the yoga group practiced yoga (breathing techniques, postures, guided relaxation and chanting), 45 minutes each day, 5 days a week. During this time the

physical exercise group had jogging-in-place, rapid repetitive movements and relay races or games. Both groups were assessed at the end of 3 months. Data were analyzed with RM ANOVA and post-hoc tests were Bonferroni adjusted.

RESULTS: There was one significant difference between groups. This was in social self-esteem which was higher after physical exercise compared to yoga ($p < 0.05$). All the changes reported below are based on after-before comparisons, within each group. Both groups showed an increase in BMI, and number of sit-ups ($p < 0.001$). Balance worsened in the physical exercise group, while plate tapping improved in the yoga group ($p < 0.001$). In the Stroop task both groups showed improved color, word- and color-word naming ($p < 0.01$), while the physical exercise group showed higher interference scores. Total, general and parental self-esteem improved in the yoga group ($p < 0.05$).

CONCLUSION:
Yoga and physical exercise are useful additions to the school routine, with physical exercise improving social self-esteem.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24199742/

Ann N Y Acad Sci. 2014 Jan;1308:149-61. doi: 10.1111/nyas.12367.

Cost effectiveness of responsive stimulation and nutrition interventions on early child development outcomes in Pakistan.

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Early childhood programs are heralded as a way to improve children's health and educational outcomes. However, few studies in developing countries calculate the effectiveness of quality early childhood interventions. Even fewer estimate the associated costs of such interventions. **The study here looks at the costs and effectiveness of a cluster-randomized effectiveness trial on children from birth to 24 months in rural Sindh, Pakistan. Responsive stimulation and/or enhanced nutrition interventions were integrated in the Lady Health Worker program in Pakistan.** Outcomes suggest that children who receive responsive stimulation had significantly better development outcomes at 24 months than those who only received enhanced nutrition intervention. A cost-effectiveness analysis of the results verifies that early childhood interventions that include responsive stimulation are more cost effective than a nutrition intervention alone in promoting children's early development. Costs of a responsive stimulation intervention integrated in an existing community-based service providing basic health and nutrition care is approximately US$4 per month per child. We discuss these findings and make recommendations about scaling up and costs for future early child development programs.

Comment
What is responsive stimulation? Another study from Bangladesh described it thus: "Messages that mothers discuss and practice with children: hand-washing, self-feeding, maternal verbal responsivity, solutions to child refusals, dietary diversity, and responsive stimulation during play. The behaviour change strategy, based on components of social-cognitive learning theory, included practice, problem solving, and peer support. Training may involve demonstration of

the behaviour by the peer educator with one child and then coaching mothers as they practiced with their own child. Mothers may be asked to bring a play bag and to gradually fill it with home materials for play (eg, cloth, spoons, sticks, pictures).”
http://pediatrics.aappublications.org/content/127/5/e1191.full.pdf

Res Dev Disabil. 2013 Oct;34(10):3112-23. doi: 10.1016/j.ridd.2013.06.037. Epub 2013 Jul 22.

A randomized controlled trial of routines-based early intervention for children with or at risk for developmental delay.

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Routines-based early intervention (RBEI) for children with or at risk for developmental delay encourages collaboration between professionals and families to enhance children's participation in family routines with family-selected goals. We conducted the first single-blinded randomized control trial to examine the effectiveness of a 6-month RBEI vs. traditional home visiting (THV), which uses a curriculum focused on children's developmental domains. **Thirty-one families with children aged 5-30 months (mean age 17.4 months) with or at risk for developmental delay were randomly assigned to an RBEI group (n=15) or a THV group (n=16).** The enrolled children were evaluated using the Chinese version of Pediatric Evaluation of Disability Inventory (PEDI-C) and the Comprehensive Development Inventory for Infants and Toddlers (CDIIT) at 5 time points. Two-way mixed analysis of variance (ANOVA) was used to examine the group by stage interactions. Goal Attainment Scaling (GAS) and the Canadian Occupational Performance Measure (COPM) were applied to explore between-group differences on individualized goal achievement. PEDI-C showed that the RBEI group had a faster progress rate in self-care functions and independence in social functions in the first 3 months of intervention and at the 6-month follow-up. The RBEI group also scored higher on the GAS in the first 3 months of intervention. However, between-group differences in changes in the developmental domains on the CDIIT were not significant. Thus, **RBEI was more effective than THV in promoting functional outcomes and reaching family-selected goals, while both interventions allowed equal improvement in developmental domains.**

http://linkinghub.elsevier.com/retrieve/pii/S0891-4222(13)00286-2

Comment
What is “Routines-based intervention”? Apparently it is early intervention that is embedded within normal family routines, care practise and play, rather than separate therapy given only when the child is having “early intervention”. Makes sense.

Autism Res. 2014 Feb;7(1):145-61. doi: 10.1002/aur.1354. Epub 2014 Jan 9.

A randomized controlled trial of the Korean version of the PEERS(®) parent-assisted social skills training program for teens with ASD.

Randomised trials in child health in developing countries 2013-14

Yoo HJ[1], Bahn G, Cho IH, Kim EK, Kim JH, Min JW, Lee WH, Seo JS, Jun SS, Bong G, Cho S, Shin MS, Kim BN, Kim JW, Park S, Laugeson EA.

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Impaired social functioning is a hallmark feature of autism spectrum disorder (ASD), often requiring treatment throughout the life span. PEERS(®) (Program for the Education and Enrichment of Relational Skills) is a parent-assisted social skills training for teens with ASD. Although PEERS(®) has an established evidence base in improving the social skills of adolescents and young adults with ASD in North America, the efficacy of this treatment has yet to be established in cross-cultural validation trials. The objective of this study is to examine the feasibility and treatment efficacy of a Korean version of PEERS(®) for enhancing social skills through a randomized controlled trial (RCT).The English version of the PEERS(®) Treatment Manual (Laugeson & Frankel, 2010) was translated into Korean and reviewed by 21 child mental health professionals. Items identified as culturally sensitive were surveyed by 447 middle school students, and material was modified accordingly. Participants included 47 teens between 12 and 18 years of age with a diagnosis of ASD and a verbal intelligence quotient (IQ) ≥ 65. **Eligible teens were randomly assigned to a treatment group (TG) or delayed treatment control group (CG).** Primary outcome measures included questionnaires and direct observations quantifying social ability and problems directly related to ASD. Secondary outcome measures included scales for depressive symptoms, anxiety, and other behavioral problems. Rating scales for parental depressive symptoms and anxiety were examined to detect changes in parental psychosocial functioning throughout the PEERS(®) treatment. Independent samples t-tests revealed no significant differences at baseline across the TG and CG conditions with regard to age (14.04 ± 1.64 and 13.54 ± 1.50 years), IQ (99.39 ± 18.09 & 100.67 ± 16.97), parental education, socioeconomic status, or ASD symptoms ($p < 0.05$), respectively. **Results for treatment outcome suggest that the TG showed significant improvement in communication and social interaction domain scores on the Autism Diagnostic Observation Schedule, interpersonal relationship and play/leisure time on the subdomain scores of the Korean version of the Vineland Adaptive Behavior Scale (p's < 0.01), social skills knowledge total scores on the Test of Adolescent Social Skills Knowledge-Revised (p < 0.01), and decreased depressive symptoms on the Child Depression Inventory following treatment (p < 0.05).** Analyses of parental outcome reveal a significant decrease in maternal state anxiety in the TG after controlling for potential confounding variables ($p < 0.05$). Despite cultural and linguistic differences, the PEERS(®) social skills intervention appears to be efficacious for teens with ASD in Korea with modest cultural adjustment. In an RCT, participants receiving the PEERS(®) treatment showed significant improvement in social skills knowledge, interpersonal skills, and play/leisure skills, as well as a decrease in depressive symptoms and ASD symptoms. This study represents one of only a few cross-cultural validation trials of an established evidence-based treatment for adolescents with ASD.

Comment
The PEERS program is a US-based initiative from UCLA, it is described at:
http://www.semel.ucla.edu/peers

Diarrhoea

(See also Zinc, Vaccines and immunization - Rotavirus vaccine, Environmental health, hand-washing and sanitation)

Pediatrics. 2013 Oct;132(4):e832-40. doi: 10.1542/peds.2012-3986. Epub 2013 Sep 9.

Vitamin D_3 supplementation and childhood diarrhea: a randomized controlled trial.

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OBJECTIVE:
To investigate the effect of vitamin D3 supplementation on the incidence and risk for first and recurrent diarrheal illnesses among children in Kabul, Afghanistan.

METHODS: This double-blind placebo-controlled trial randomized **3046 high-risk 1- to 11-month-old infants to receive 6 quarterly doses of oral vitamin D3 (cholecalciferol 100000 IU) or placebo in inner city Kabul.** Data on diarrheal episodes (≥ 3 loose/liquid stools in 24 hours) was gathered through active and passive surveillance over 18 months of follow-up. Time to first diarrheal illness was analyzed by using Kaplan-Meier plots. Incidence rates and hazard ratios (HRs) were calculated by using recurrent event Poisson regression models.

RESULTS: No significant difference existed in survival time to first diarrheal illness (log rank P = .55). **The incidences of diarrheal episodes were 3.43 (95% confidence interval [CI], 3.28-3.59) and 3.59 per child-year (95% CI, 3.44-3.76) in the placebo and intervention arms, respectively.** Vitamin D3 supplementation was found to have no effect on the risk for recurrent diarrheal disease in either intention-to-treat (HR, 1.05; 95% CI, 0.98-1.17; P = .15) or per protocol (HR, 1.05; 95% CI, 0.98-1.12; P = .14) analyses. The lack of preventive benefit remained when the randomized population was stratified by age groups, nutritional status, and seasons.

CONCLUSIONS: **Quarterly supplementation with vitamin D3 conferred no reduction on time to first illness or on the risk for recurrent diarrheal disease in this study.** Similar supplementation to comparable populations is not recommended. Additional research in alternative settings may be helpful in elucidating the role of vitamin D3 supplementation for prevention of diarrheal diseases.

Pediatrics. 2013 Jul;132(1):e46-52. doi: 10.1542/peds.2012-2980. Epub 2013 Jun 3.

Short-course prophylactic zinc supplementation for diarrhea morbidity in infants of 6 to 11 months.

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BACKGROUND: Zinc supplementation during diarrhea substantially reduces the incidence and severity of diarrhea. However, the effect of short-course zinc prophylaxis has been observed only in children >12 months of age. Because the incidence of diarrhea is comparatively high in children aged 6 to 11 months, we assessed the prophylactic effect of zinc on incidence and duration of diarrhea in this age group.

METHODS: In this randomized, double-blind, placebo-controlled trial, we enrolled **infants aged 6 to 11 months from an urban resettlement colony in Delhi, India,** between January 1, 2011, and January 15, 2012. **We randomly assigned 272 infants to receive either 20 mg of zinc or a placebo suspension orally every day for 2 weeks.** The primary outcome was the incidence of diarrhea per child-year. All analyses were done by intention-to-treat.

RESULTS: **A total of 134 infants in the zinc and 124 in the placebo groups were assessed for the incidence of diarrhea. There was a 39% reduction (crude incident rate ratio [IRR] 0.61, 95% confidence interval [CI] 0.53-0.71) in episodes of diarrhea, 39% (adjusted IRR 0.61, 95% CI 0.54-0.69) in the total number of days that a child suffered from diarrhea, and reduction of 36% in duration per episode of diarrhea (IRR 0.64, 95% CI 0.56-0.74) during the 5 months of follow-up.**

CONCLUSIONS: Short-course prophylactic zinc supplementation for 2 weeks may reduce diarrhea morbidity in infants of 6 to 11 months for up to 5 months, in populations with high prevalence of wasting and stunting.

http://pediatrics.aappublications.org/cgi/pmidlookup?view=long&pmid=23733798

Indian J Med Res. 2014 Mar;139(3):379-85.

Lactobacillus GG for treatment of acute childhood diarrhoea: an open labelled, randomized controlled trial.

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BACKGROUND & OBJECTIVES: Randomized controlled trials in developed countries have reported benefits of Lactobacillus GG (LGG) in the treatment of acute watery diarrhoea, but there is paucity of such data from India. The study was aimed to evaluate the efficacy and safety of Lactobacillus GG in the treatment of acute diarrhoea in children from a semi-urban city in north India.

METHODS: In this open labelled, randomized controlled trial 2000 children with acute watery diarrhoea, aged between 6 months to 5 years visiting outpatient department and emergency room of a teaching hospital in north India were enrolled. **The children were randomized into receiving either Lactobacillus GG in dose of 10 billion cfu/day for five days or no probiotic medication in addition to standard WHO management of diarrhoea.** Primary outcomes were duration of diarrhoea and time to change in consistency of stools.

RESULTS: **Median (inter quartile range) duration of diarrhoea was significantly shorter in children in LGG group [60 (54-72) h vs. 78 (72-90) h; P<0.001].** Also, there was faster improvement in stool consistency in children receiving Lactobacillus GG than control group [36 (30-36) h vs. 42 (36-48) h; P<0.001]. There was significant reduction in average number of stools per day in LGG group (P<0.001) compared to the control group. These benefits were seen irrespective of rotavirus positivity in stool tests.

INTERPRETATION & CONCLUSIONS: **Our results showed that the use of Lactobacillus GG in children with acute diarrhoea resulted in shorter duration and faster improvement in stool consistency** as compared to the control group.

http://www.ijmr.org.in/temp/IndianJMedRes1393379-2260283_061642.pdf

Clin Infect Dis. 2014 Apr;58(8):1107-15. doi: 10.1093/cid/ciu065. Epub 2014 Feb 5.

Immune response and intestinal permeability in children with acute gastroenteritis treated with Lactobacillus rhamnosus GG: a randomized, double-blind, placebo-controlled trial.

Sindhu KN[1], Sowmyanarayanan TV, Paul A, Babji S, Ajjampur SS, Priyadarshini S, Sarkar R, Balasubramanian KA, Wanke CA, Ward HD, Kang G.

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BACKGROUND: Probiotics have a possible role in the treatment of pediatric acute gastroenteritis. We report the effect of the probiotic Lactobacillus rhamnosus GG (LGG) on intestinal function, immune response, and clinical outcomes in Indian children with cryptosporidial or rotavirus diarrhea.

METHODS: **Children with gastroenteritis aged 6 months to 5 years, testing positive for either rotavirus or Cryptosporidium species in stool (coinfections were excluded), were randomized to LGG (ATCC 53103) or placebo, once daily for 4 weeks**. Baseline demographic and clinical details were obtained. Sera were tested for immunoglobulin G (IgG) and immunoglobulin A (IgA) antibodies to Cryptosporidium and rotavirus, and the lactulose to mannitol ratio for intestinal permeability was determined at baseline and at the end of follow-up.

RESULTS: Of the 124 children enrolled, 82 and 42 had rotavirus and cryptosporidial diarrhea, respectively. Median diarrheal duration was 4 days; one-third of the children had severe diarrhea. Baseline and clinical parameters were comparable between children receiving LGG and placebo. **At the end of follow-up, fewer children with rotavirus diarrhea on LGG had repeated diarrheal episodes (25% vs 46%; P = .048) and impaired intestinal function (48% vs 72%; P = .027).** Significant increase in IgG levels postintervention (456 vs 2215 EU; P = .003) was observed in children with rotavirus diarrhea receiving LGG. Among children with cryptosporidial diarrhea, those receiving LGG showed significant improvement in intestinal permeability.

CONCLUSIONS: LGG has a positive immunomodulatory effect and may be useful in decreasing repeated episodes of rotavirus diarrhea. Improvement in intestinal function in children with rotavirus and cryptosporidial gastroenteritis emphasizes the role of probiotics in treating intestinal impairment after infection.

Southeast Asian J Trop Med Public Health. 2013 Nov;44(6):1065-71.

Cost-benefit analysis of the probiotic treatment of children hospitalized for acute diarrhea in Bangkok, Thailand.

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We studied the cost-benefit of using probiotics (Lactobacillus acidophilus and Bifidobacterium bifidum) in the treatment of 106 children hospitalized with acute diarrhea using a double-blind randomized, placebo-controlled trial. **The median length of hospital stay was significantly shorter in the probiotics group than in the controlled group (2 versus 3 days, p=0.049),** but the median duration of diarrhea and direct medical costs were not significantly different (4 versus 5 days, p=0.068 and 4,418.75 versus 4,778.75 Thai Baht, p=0.342). Taking into consideration parental income loss, a non-significant lower expense was seen in the probiotics group (6,800.33 versus 7,970.92 Thai Baht, p=0.177). A greater cost-benefit with the probiotic treatment is probable, but was not statistically significant in this small study. In conclusion, the probiotics tested shortened the duration of hospitalization of children with diarrhea but the total expenses were not different.

J Pharmacol Pharmacother. 2013 Jul;4(3):205-8. doi: 10.4103/0976-500X.114603.

Comparison of efficacy of Saccharomyces boulardii strain in the treatment of acute diarrhea in children: A prospective, single-blind, randomized controlled clinical trial.

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http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23960427/

Water purification

Am J Trop Med Hyg. 2013 Dec;89(6):1190-4. doi: 10.4269/ajtmh.13-0054. Epub 2013 Oct 7.

Follow-up study to assess the use and performance of household filters in Zambia.

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Effective household water treatment can improve drinking water quality and prevent disease if used correctly and consistently over time. **One year after completion of a randomized controlled study of water filters among households in Zambia with children < 2 years old and mothers who were human immunodeficiency virus (HIV)-positive, we conducted a follow-up study to assess use and performance of new filters distributed at the conclusion of the study**; **90% of participating households met the criteria for current users, and 75% of participating households had stored water with lower levels of fecal contamination than source water. Microbiologically, the filters continued to perform well, removing an average of 99.0% of fecal indicator bacteria.** Although this study provides some encouraging evidence about the potential to maintain high uptake and filter performance, even in the absence of regular household visits, additional research is necessary to assess whether these results can be achieved over longer periods and with larger populations.

Comment
This is an important study. Many RCTs are not followed-up but this study showed the sustained effect of water filters in providing clean water to households in Zambia a year after the RCT.

PLoS Med. 2013 Aug;10(8):e1001497. doi: 10.1371/journal.pmed.1001497. Epub 2013 Aug 20.

Effect of household-based drinking water chlorination on diarrhoea among children under five in Orissa, India: a double-blind randomised placebo-controlled trial.

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BACKGROUND: Boiling, disinfecting, and filtering water within the home can improve the microbiological quality of drinking water among the hundreds of millions of people who rely on unsafe water supplies. However, the impact of these interventions on diarrhoea is unclear. Most studies using open trial designs have reported a protective effect on diarrhoea while blinded studies of household water treatment in low-income settings have found no such effect. However, none of those studies were powered to detect an impact among children under five and participants were followed-up over short periods of time. The aim of this study was to measure the effect of in-home water disinfection on diarrhoea among children under five.

METHODS AND FINDINGS: We conducted a double-blind randomised controlled trial between November 2010 and December 2011. The study included 2,163 households and 2,986 children under five in rural and urban communities of Orissa, India. **The intervention consisted of an intensive promotion campaign and free distribution of sodium dichloroisocyanurate (NaDCC) tablets during bi-monthly households visits.** An independent evaluation team visited households monthly for one year to collect health data and water samples. **The primary outcome was the longitudinal prevalence of diarrhoea (3-day point prevalence) among children aged under five.** Weight-for-age was also measured at each visit to assess its potential as a proxy marker for diarrhoea. Adherence was monitored each month through caregiver's reports and the presence of residual free chlorine in the child's drinking water at the time of visit.

On 20% of the total household visits, children's drinking water was assayed for thermotolerant coliforms (TTC), an indicator of faecal contamination. The primary analysis was on an intention-to-treat basis. Binomial regression with a log link function and robust standard errors was used to compare prevalence of diarrhoea between arms. We used generalised estimating equations to account for clustering at the household level. The impact of the intervention on weight-for-age z scores (WAZ) was analysed using random effect linear regression. Over the follow-up period, 84,391 child-days of observations were recorded, representing 88% of total possible child-days of observation. **The longitudinal prevalence of diarrhoea among intervention children was 1.69% compared to 1.74% among controls. After adjusting for clustering within household, the prevalence ratio of the intervention to control was 0.95 (95% CI 0.79-1.13).** The mean WAZ was similar among children of the intervention and control groups (-1.586 versus -1.589, respectively). Among intervention households, 51% reported their child's drinking water to be treated with the tablets at the time of visit, though only 32% of water samples tested positive for residual chlorine. Faecal contamination of drinking water was lower among intervention households than controls (geometric mean TTC count of 50 [95% CI 44-57] per 100 ml compared to 122 [95% CI 107-139] per 100 ml among controls [p<0.001] [n=4,546]).

CONCLUSIONS: Our study was designed to overcome the shortcomings of previous double-blinded trials of household water treatment in low-income settings. The sample size was larger, the follow-up period longer, both urban and rural populations were included, and adherence and water quality were monitored extensively over time. **These results provide no evidence that the intervention was protective against diarrhoea.** Low compliance and modest reduction in water contamination may have contributed to the lack of effect. However, our findings are consistent with other blinded studies of similar interventions and raise additional questions about the actual health impact of household water treatment under these conditions.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23976883/

Endocrine disorders, vitamin D and bone health

Indian Pediatr. 2014 Apr;51(4):265-72.

300,000 IU or 600,000 IU of oral vitamin D3 for treatment of nutritional rickets: a randomized controlled trial.

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OBJECTIVE:
To evaluate the non-inferiority of a lower therapeutic dose (300,000 IU) in comparison to standard dose (600,000) IU of Vitamin D for increasing serum 25(OH) D levels and achieving radiological recovery in nutritional rickets.

DESIGN: Randomized, open-labeled, controlled trial.

SETTING: Tertiary care hospital.

PARTICIPANTS: 76 children (median age 12 mo) with clinical and radiologically confirmed rickets.

INTERVENTION: **Oral vitamin D3 as 300,000 IU (Group 1; n=38) or 600,000 IU (Group 2; n=38) in a single day.**

OUTCOME VARIABLES: Primary: Serum 25(OH)D, 12 weeks after administration of vitamin D3; Secondary: Radiological healing and serum parathormone at 12 weeks; and clinical and biochemical adverse effects.

RESULTS: Serum 25(OH)D levels [geometric mean (95% CI)] increased significantly from baseline to 12 weeks after therapy in both the groups [Group 1: 7.58 (5.50–10.44) to 16.06 (12.71– 20.29) ng/mL, P<0.001]; Group 2: 6.57 (4.66–9.25) to 17.60 (13.71–22.60, P<0.001]. The adjusted ratio of geometric mean serum 25(OH)D levels at 12 weeks between the groups (taking baseline value as co-variate) was 0.91 (95% CI: 0.65–1.29). **Radiological healing occurred in all children by 12 weeks.** Both groups demonstrated significant (P<0.05) and comparable fall in the serum parathormone and alkaline phosphatase levels at 12 weeks. Relative change [ratio of geometric mean (95% CI)] in serum PTH and alkaline phosphatase, 12 weeks after therapy, were 0.98 (0.7–1.47) and 0.92 (0.72–1.19), respectively. The serum 25(OH)D levels were deficient (<20 ng/mL) in 63% (38/60) children after 12 weeks of intervention [Group 1: 20/32 (62.5%); Group 2: 18/28 (64.3%)]. No major clinical adverse effects were noticed in any of the children. Hypercalcemia was documented in 2 children at 4 weeks (1 in each Group) and 3 children at 12 weeks (1 in Group 1 and 2 in Group 2). None of the participants had hypercalciuria or hypervitaminosis D.

CONCLUSION: **A dose of 300,000 IU of vitamin D3 is comparable to 600,000 IU, administered orally, over a single day, for treating rickets in under-five children although there is an unacceptably high risk of hypercalcemia in both groups**. None of the regime is effective in normalization of vitamin D status in majority of patients, 3 months after administering the therapeutic dose.

J Trop Pediatr. 2014 Jun;60(3):203-10. doi: 10.1093/tropej/fmt105. Epub 2014 Jan 8.

A Randomized Controlled Trial on Safety and Efficacy of Single Intramuscular versus Staggered Oral Dose of 600 000IU Vitamin D in Treatment of Nutritional Rickets.

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OBJECTIVE:
Comparison of efficacy and safety of two different regimens of vitamin D-600 000 IU as a single intramuscular dose, and 60 000IU orally once a week for 10 weeks-in treatment of nutritional rickets.

METHODS: **Children with nutritional rickets (age: 0.5-5 years, n = 61) were randomized to receive either 60 000IU vitamin D orally once a week for 10 weeks or 600 000IU single intramuscular injection.** Serum calcium, phosphate, alkaline phosphatase, urinary calcium/creatinine ratio, serum 25 hydroxy vitamin D and radiological score were compared at 12-week follow-up.

RESULTS: No difference was found in efficacy of the two regimens on comparing biochemical and radiological parameters. Serum 25 hydroxy vitamin D >100 ng/ml was found in two children in the oral group and one child in the intramuscular group. No child developed hypercalcemia or hypercalciuria after starting treatment.

CONCLUSION: **Staggered oral and one-time intramuscular administrations of 600 000IU vitamin D are equally effective and safe in treatment of nutritional rickets**.

J Clin Endocrinol Metab. 2014 Jan;99(1):126-32. doi: 10.1210/jc.2013-2502. Epub 2013 Dec 20.

24-month use of once-weekly GH, LB03002, in prepubertal children with GH deficiency.

Khadilkar V[1], Radjuk KA, Bolshova E, Khadgawat R, El Kholy M, Desai M, Peterkova V, Mericq V, Kratzsch J, Siepl EC, Martin D, Lopez P, Ji HJ, Bae YJ, Lee JH, Saenger PH.

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BACKGROUND: Sustained-release GH formulations may provide a strategy for improving treatment compliance and persistence in GH-deficient patients.

OBJECTIVE: The aim of the study was to examine efficacy and safety of LB03002, a sustained-release GH formulation for once-weekly administration.

DESIGN: We conducted a phase III, 12-month, multinational, randomized, open-label, comparator-controlled trial with a 12-month uncontrolled extension.

PATIENTS: Prepubertal GH treatment-naive GH-deficient children (mean age, 7.8 y) participated in the study.

INTERVENTION: **We administered once-weekly LB03002 (n=91) or daily GH (n=87) for 1 year, followed by once-weekly LB03002 for all patients for another year (LB03002 throughout, n=87; switched to LB03002, n=80).**

OUTCOME MEASURES: Height, height velocity (HV), IGF-1, GH antibodies, and adverse events were determined throughout. Primary analysis was noninferiority of LB03002 vs daily GH at 1 year by analysis of covariance.

RESULTS: Mean±SD HV during year 1 was 11.63±2.60 cm/y with LB03002, and 11.97±3.09 cm/y with daily GH, with increases from baseline of 8.94±2.91 and 9.04±3.19 cm/y, respectively. The least square mean HV difference for LB03002 - daily GH was -0.43 cm/y (99% confidence interval, -1.45 to 0.60 cm/y). Mean HV also remained above baseline in year 2 (8.33±1.92 cm/y in the LB03002 throughout group, and 7.28±2.34 cm/y in the switched to LB03002 group). Injection site reactions occurred more frequently in LB03002-treated patients but were considered mild to moderate in >90% of cases.

CONCLUSIONS: Growth response with once-weekly LB03002 in GH-deficient children is comparable to that with daily GH, achieving expected growth rates for 24 months. Once-weekly LB03002 is a strong candidate for long-term GH replacement in GH-deficient children.

Eur J Endocrinol. 2013 Jul 6;169(2):179-85. doi: 10.1530/EJE-13-0148. Print 2013 Aug.

Efficacy and safety of LB03002, a once-weekly sustained-release human GH for 12-month treatment in Korean children with GH deficiency.

Hwang JS[1], Lee HS, Chung WY, Han HS, Jin DK, Kim HS, Ko CW, Lee BC, Lee DY, Lee KH, Shin JH, Suh BK, Yoo HW, Ji HJ, Lee JH, Bae YJ, Kim DH, Yang SW.

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PURPOSE: The purpose of this study was to investigate the efficacy and safety of LB03002, a sustained-release human GH (SR-hGH), compared with that of daily rhGH for 12 months in children with GH deficiency (GHD).

METHODS: **A total of 73 children with GHD were screened and 63 eligible subjects were randomized in a 1:1 ratio of LB03002 (SR-hGH) to daily rhGH treatment group. LB03002 was administered once weekly at a dose of 0.5 mg/kg while daily rhGH was administered for 6 consecutive days with equally divided doses to make a total of 0.21 mg/kg per week**. Treatments were given for 12 months by s.c. injections. Injection site reactions and adverse events were investigated throughout the study period.

RESULTS: The mean (S.D.) height velocity (HV) SHOWED a clinically significant increase after the 6-month treatment: 3.00 (1.15) cm/year at screening to 9.78 (1.98) cm/year at 6 months in the LB03002 group; 2.39 (1.63) cm/year at screening to 10.56 (2.65) cm/year at 6 months in the daily rhGH group. The increased HV at 12 months was still maintained in both the groups: 9.06 (1.63) cm/year at 12 months in the LB03002 group; 9.72 (2.32) cm/year at 12 months in the daily rhGH group. Most of the adverse drug reactions were mild and tolerable. No subjects were withdrawn due to adverse events.

CONCLUSION: **Weekly injection of LB03002 at a dose of 0.5 mg/kg per week was confirmed to have comparable efficacy to daily injection of rhGH at a dose of 0.21 mg/kg per week**. Both formulations were well tolerated.

Epilepsy and acute seizures

Epilepsia. 2014 Feb;55(2):344-52. doi: 10.1111/epi.12498. Epub 2014 Jan 21.

Evaluation of Kilifi epilepsy education programme: a randomized controlled trial.

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OBJECTIVES:
The epilepsy treatment gap is largest in resource-poor countries. We evaluated the efficacy of a 1-day health education program in a rural area of Kenya. The primary outcome was adherence to antiepileptic drugs (AEDs) as measured by drug levels in the blood, and the secondary outcomes were seizure frequency and Kilifi Epilepsy Beliefs and Attitudes Scores (KEBAS).

METHODS: **Seven hundred thirty-eight people with epilepsy (PWE) and their designated supporter were randomized to either the intervention (education) or nonintervention group**. Data were collected at baseline and 1 year after the education intervention was administered to the intervention group. There were 581 PWE assessed at both time points. At the end of the study, 105 PWE from the intervention group and 86 from the nonintervention group gave blood samples, which were assayed for the most commonly used AEDs (phenobarbital, phenytoin, and carbamazepine). The proportions of PWE with detectable AED levels were determined using a standard blood assay method. The laboratory technicians conducting the assays were blinded to the randomization. Secondary outcomes were evaluated using questionnaires administered by trained field staff. Modified Poisson regression was used to investigate the factors associated with improved adherence (transition from nonoptimal AED level in blood at baseline to optimal levels at follow-up), reduced seizures, and improved KEBAS, which was done as a post hoc analysis. This trial is registered in ISRCTN register under ISRCTN35680481.

RESULTS: **There was no significant difference in adherence to AEDs based on detectable drug levels (odds ratio [OR] 1.46, 95% confidence interval [95% CI] 0.74-2.90, p = 0.28) or by self-reports (OR 1.00, 95% CI 0.71-1.40, p = 1.00) between the intervention**

and nonintervention group. The intervention group had significantly fewer beliefs about traditional causes of epilepsy, cultural treatment, and negative stereotypes than the nonintervention group. There was no difference in seizure frequency. A comparison of the baseline and follow-up data showed a significant increase in adherence-intervention group (36-81% [p < 0.001]) and nonintervention group (38-74% [p < 0.001])-using detectable blood levels. The number of patients with less frequent seizures (≤3 seizures in the last 3 months) increased in the intervention group (62-80% [p = 0.002]) and in the nonintervention group (67-75% [p = 0.04]). Improved therapeutic adherence (observed in both groups combined) was positively associated with positive change in beliefs about risks of epilepsy (relative risk [RR] 2.00, 95% CI 1.03-3.95) and having nontraditional religious beliefs (RR 2.01, 95% CI 1.01-3.99). Reduced seizure frequency was associated with improved adherence (RR 1.72, 95% CI 1.19-2.47). Positive changes in KEBAS were associated with having tertiary education as compared to none (RR 1.09, 95% CI 1.05-1.14).

SIGNIFICANCE:
Health education improves knowledge about epilepsy, but once only contact does not improve adherence. However, sustained education may improve adherence in future studies.

http://onlinelibrary.wiley.com/store/10.1111/epi.12498/asset/epi12498.pdf?v=1&t=hxd2gfr5&s=310afa9f377651b533050a81fc766ccc200fece0

J Child Neurol. 2013 Jul 31. [Epub ahead of print]

Efficacy of Sublingual Lorazepam Versus Intrarectal Diazepam for Prolonged Convulsions in Sub-Saharan Africa.

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In Sub-Saharan Africa, intrarectal diazepam is the first-line anticonvulsant mostly used in children. We aimed to assess this standard care against sublingual lorazepam, a medication potentially as effective and safe, but easier to administer. **A randomized controlled trial was conducted in the pediatric emergency departments of 9 hospitals. A total of 436 children aged 5 months to 10 years with convulsions persisting for more than 5 minutes were assigned to receive intrarectal diazepam (0.5 mg/kg, n = 202) or sublingual lorazepam (0.1 mg/kg, n = 234). Sublingual lorazepam stopped seizures within 10 minutes of administration in 56% of children compared with intrarectal diazepam in 79% (P < .001).** The probability of treatment failure is higher in case of sublingual lorazepam use (OR = 2.95, 95% CI = 1.91-4.55). **Sublingual lorazepam is less efficacious in stopping pediatric seizures than intrarectal diazepam, and intrarectal diazepam should thus be preferred as a first-line medication in this setting.**

J Pharmacol Pharmacother. 2014 Apr;5(2):93-9. doi: 10.4103/0976-500X.130048.

Folic acid supplementation on homocysteine levels in children taking antiepileptic drugs: A randomized controlled trial.

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OBJECTIVES: To assess the level of homocysteine (tHcy) in children taking AEDs and to study whether daily oral supplementation of folic acid for 1 month will reduce the tHcy level.

MATERIALS AND METHODS: This was a double-blinded, randomized control trial conducted in Institute of Maternal and Child Health, Kozhikode, India. Totally 60 children were recruited and of them, 48 were enrolled. Of these children, 32 were assigned to the experimental group and 16 to the control group. Baseline data collection and tHcy estimation were done. One mg folic acid tablets were given to the experimental group and placebo tablets to the control group for 30 days. tHcy levels were re-estimated after 1 month follow-up. Statistical significance was tested by $\chi(2)$ test, and paired and unpaired t-tests, as appropriate. Correlation was tested by Pearson correlation test and P value less than 0.05 was taken as the cut-off for statistical significance.

RESULTS: Baseline plasma tHcy concentrations in both groups were comparable [11.90 (6.3) and 13.02 (2.4) μmol/l, respectively]. During the follow-up period, no increase in seizure episodes or no serious adverse reactions were noticed in either group. The reduction of tHcy in the experimental group was 1.92 μmol/l ($P = 0.04$) and in the control group, there was an increase of 1.05 μmol/l ($P = 0.16$).

CONCLUSIONS: In children on AED treatment, folic acid supplementation may reduce tHcy level and thus reduce CVD risk.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24799812/

Comment

Enzyme-inducing antiepileptic drugs (such as phenytoin and phenobarbitone) raise homocysteine levels, directly and secondary to depletin of folic acid. High homocysteine levels can lead to cerebovascular disease. So children on these anti-epileptic drugs should also be on folic acid supplementation.

Hygiene and environmental health

Trop Med Int Health. 2014 Mar;19(3):284-92. doi: 10.1111/tmi.12254. Epub 2014 Jan 2.

An investigation of the effects of a hand washing intervention on health outcomes and school absence using a randomised trial in Indian urban communities.

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OBJECTIVES: To evaluate how an intervention, which combined **hand washing promotion aimed at 5-year-olds with provision of free soap**, affected illnesses among the children and their families and children's school absenteeism.

METHODS: We monitored illnesses, including diarrhoea and acute respiratory infections (ARIs), school absences and soap consumption for 41 weeks in 70 low-income communities in Mumbai, India (35 communities per arm).

RESULTS: Outcomes from 847 intervention households (containing 847 5-year-olds and 4863 subjects in total) and 833 control households (containing 833 5-year-olds and 4812 subjects) were modelled using negative binomial regression. **Intervention group 5-year-olds had fewer episodes of diarrhoea (-25%, 95% confidence intervals [CI] = -37%, -2%), ARIs (-15%, 95% CI = -30%, -8%), school absences due to illnesses (-27%, 95% CI = -41%, -18%) and eye infections (-46%, 95% CI = -58%, -31%).** Further, there were fewer episodes of diarrhoea and ARIs in the intervention group for 'whole families' (-31%, 95% CI = -37%, -5%; and -14%, 95% CI = -23%, -6%, respectively), 6- to 15-year-olds (-30%, 95% CI = -39%, -7%; and -15%, 95% CI = -24%, -6%) and under 5 s (-32%, 95% CI = -41%, -4%; and -20%, 95% CI = -29%, -8%).

CONCLUSIONS: Direct-contact hand washing interventions aimed at younger school-aged children can affect the health of the whole family. These may be scalable through public-private partnerships and classroom-based campaigns. Further work is required to understand the conditions under which health benefits are transferred and the mechanisms for transference.

Haematological disorders

Blood Coagul Fibrinolysis. 2013 Jul;24(5):505-9. doi: 10.1097/MBC.0b013e32835e5337.

A comparison of intravenous immunoglobulin (2 g/kg totally) and single doses of anti-D immunoglobulin at 50 µg/kg, 75 µg/kg in newly diagnosed children with idiopathic thrombocytopenic purpura: Ankara hospital experience.

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We conducted this prospective randomized trial of **intravenous immunoglobulin (IVIG) treatment in children with newly diagnosed immune thrombocytopenic purpura (ITP) to compare the efficacy of IVIG to standard and higher doses of anti-D IVIG**. Seventy-eight patients who were previously untreated and between the age of 1 and 18 years with newly diagnosed acute ITP and a platelet concentration less than 20×10/l were eligible for enrollment. In this study IVIG treatment was compared with two different doses of anti-D. Study patients were randomized to receive treatment according to one of the two single anti-D IVIG doses [50 μg/kg (n=19) or 75 μg/kg (n=20)] or 2 g/kg (400 mg/kg per day, 5 day) total dose of IVIG (n=39). There is a significant increase of 24th hour, 48th hour, 72nd hour, 7th day and 30th day platelet counts in IVIG (2 g/kg, total dose) group compared to anti-D IVIG 50 μg/kg and anti-D IVIG 75 μg/kg groups. However, there were no difference between 24th hour, 48th hour, 72nd hour, 7th day and 30th day platelet counts across anti-D IVIG 50 μg/kg and anti-D IVIG 75 μg/kg groups. **In conclusion, this study suggests that IVIG is well tolerated and significantly more effective than standard and high-dose anti-D IVIG for the treatment of newly diagnosed ITP in children.** Apart from this, we believe that IVIG might be the first-line treatment of these patients. Regarding this issue further prospective studies comparing different IVIG treatment regimens with anti-D IVIG treatment regimens are needed.

Blood. 2014 Jan 16;123(3):317-25. doi: 10.1182/blood-2013-10-529974. Epub 2013 Nov 13.

Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A.

Mahlangu J[1], Powell JS, Ragni MV, Chowdary P, Josephson NC, Pabinger I, Hanabusa H, Gupta N, Kulkarni R, Fogarty P, Perry D, Shapiro A, Pasi KJ, Apte S, Nestorov I, Jiang H, Li S, Neelakantan S, Cristiano LM, Goyal J, Sommer JM, Dumont JA, Dodd N, Nugent K, Vigliani G, Luk A, Brennan A, Pierce GF; A-LONG Investigators.
Collaborators (62)

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This phase 3 pivotal study evaluated the safety, efficacy, and pharmacokinetics of a recombinant FVIII Fc fusion protein (rFVIIIFc) for prophylaxis, treatment of acute bleeding, and perioperative hemostatic control in 165 previously treated males aged ≥12 years with severe hemophilia A. The study had 3 treatment arms: arm 1, individualized prophylaxis (25-65 IU/kg every 3-5 days, n = 118); arm 2, weekly prophylaxis (65 IU/kg, n = 24); and arm 3, episodic treatment (10-50 IU/kg, n = 23). A subgroup compared recombinant FVIII (rFVIII) and rFVIIIFc pharmacokinetics. End points included annualized bleeding rate (ABR), inhibitor

development, and adverse events. The terminal half-life of rFVIIIFc (19.0 hours) was extended 1.5-fold vs rFVIII (12.4 hours; P < .001). Median ABRs observed in arms 1, 2, and 3 were 1.6, 3.6, and 33.6, respectively. In arm 1, the median weekly dose was 77.9 IU/kg; approximately 30% of subjects achieved a 5-day dosing interval (last 3 months on study). Across arms, 87.3% of bleeding episodes resolved with 1 injection. Adverse events were consistent with those expected in this population; no subjects developed inhibitors. rFVIIIFc was well-tolerated, had a prolonged half-life compared with rFVIII, and resulted in low ABRs when dosed prophylactically 1 to 2 times per week.
http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24227821/

HIV / AIDS

Ante-retroviral therapy (ART) and early infant diagnosis

J Acquir Immune Defic Syndr. 2014 May 1;66(1):e23-30. doi: 10.1097/QAI.0000000000000080.

Clinical versus rapid molecular HIV diagnosis in hospitalized African infants: a randomized controlled trial simulating point-of-care infant testing.

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OBJECTIVE: Many African infants fail to receive their diagnostic HIV molecular test results and subsequently, antiretroviral therapy (ART). To determine whether a point-of-care molecular HIV test increases ART access for hospitalized Malawian infants, we simulated a point-of-care test using rapid HIV RNA polymerase chain reaction (Rapid PCR) and compared patient outcomes with an optimized standard care that included assessment with the World Health Organization clinical algorithm for HIV infection plus a DNA PCR with a turnaround time of several weeks (standard care).

DESIGN: Randomized controlled trial.

METHODS: **Hospitalized HIV-exposed Malawian infants aged <12 months were randomized into Rapid PCR or standard care**. Rapid PCR infants obtained molecular test results within 48 hours to facilitate immediate ART, similar to a point-of-care test. Standard care infants meeting clinical criteria were also offered inpatient ART. The primary outcome was appropriate in-hospital ART for DNA or RNA PCR-confirmed HIV-infected infants.

RESULTS: Three hundred infants were enrolled. **A greater proportion of HIV-infected infants receiving Rapid PCR, versus standard care, started inpatient ART (72.3% vs 47.8%, P = 0.016)**. Among molecular test-negative infants, 26.9% receiving standard care unnecessarily initiated inpatient ART, versus 0.0% receiving Rapid PCR (P < 0.001). **Rapid PCR modestly reduced the median days to ART (3.0 vs 6.5, P = 0.001)** but did not influence outpatient follow-up for HIV-infected infants (78.1% vs 82.4%, P = 0.418).

CONCLUSIONS: Rapid PCR, versus an optimized standard care, increased the proportion of hospitalized HIV-infected infants initiating ART and reduced ART exposure in molecular test-negative infants, without meaningfully impacting time to ART initiation or follow-up rates.

Lancet. 2013 Nov 9;382(9904):1555-63. doi: 10.1016/S0140-6736(13)61409-9.

Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial.

Cotton MF, Violari A, Otwombe K, Panchia R, Dobbels E, Rabie H, Josipovic D, Liberty A, Lazarus E, Innes S, van Rensburg AJ, Pelser W, Truter H, Madhi SA, Handelsman E, Jean-Philippe P, McIntyre JA, Gibb DM, Babiker AG; CHER Study Team.

BACKGROUND: Interim results from the children with HIV early antiretroviral (CHER) trial showed that early antiretroviral therapy (ART) was life-saving for infants infected with HIV. In view of the few treatment options and the potential toxicity associated with lifelong ART, in the CHER trial we compared early time-limited ART with deferred ART.

METHODS: CHER was an open-label randomised controlled trial of HIV-infected asymptomatic infants younger than 12 weeks in two South African trial sites with a percentage of CD4-positive T lymphocytes (CD4%) of 25% or higher. **377 infants were randomly allocated to one of three groups: deferred ART (ART-Def), immediate ART for 40 weeks (ART-40W), or immediate ART for 96 weeks (ART-96W), with subsequent treatment interruption**. The randomisation schedule was stratified by clinical site with permuted blocks of random sizes to balance the numbers of infants allocated to each group. Criteria for ART initiation in the ART-Def group and re-initiation after interruption in the other groups were CD4% less than 25% in infancy; otherwise, the criteria were CD4% less than 20% or Centers for Disease Control and Prevention severe stage B or stage C disease. Combination therapy of lopinavir-ritonavir, zidovudine, and lamivudine was the first-line treatment regimen at ART initiation and re-initiation. **The primary endpoint was time to failure of first-line ART (immunological, clinical, or virological) or death.** Comparisons were done by intention-to-treat analysis, with use of time-to-event methods. This trial is registered with ClinicalTrials.gov, number NCT00102960.

FINDINGS: 377 infants were enrolled, with a median age of 7·4 weeks, CD4% of 35%, and HIV RNA log 5·7 copies per mL. Median follow-up was 4·8 years; 34 infants (9%) were lost to follow-up. Median time to ART initiation in the ART-Def group was 20 weeks (IQR 16-25).

Time to restarting of ART after interruption was 33 weeks (26-45) in ART-40W and 70 weeks (35-109) in ART-96W; at the end of the trial, 19% of patients in ART-40W and 32% of patients in ART-96W remained off ART. Proportions of follow-up time spent on ART were 81% in the ART-Def group, 70% in the ART-40W group, and 69% in the ART-96W group. **48 (38%) of 125 children in the ART-Def group, 32 (25%) of 126 in the ART-40W group, and 26 (21%) of 126 in the ART-96W group reached the primary endpoint.** The hazard ratio, relative to ART-Def, was 0·59 (95% CI 0·38-0·93, p=0·02) for ART-40W and 0·47 (0·27-0·76, p=0·002) for ART-96W. Three children in ART-Def, three in ART-40W, and one in ART-96W switched to second-line ART.

INTERPRETATION: Early time-limited ART had better clinical and immunological outcomes than deferred ART, with no evidence of excess disease progression during subsequent treatment interruption and less overall ART exposure than deferred ART. Longer time on primary ART permits longer subsequent interruption, with marginally better outcomes.

AIDS Patient Care STDS. 2013 Nov;27(11):596-603. doi: 10.1089/apc.2013.0203.

Impact of antiretroviral therapy on quality of life in HIV-infected Southeast Asian children in the PREDICT study.

Bunupuradah T, Kosalaraksa P, Vibol U, Hansudewechakul R, Sophonphan J, Kanjanavanit S, Ngampiyaskul C, Wongsawat J, Luesomboon W, Vonthanak S, Ananworanich J, Ruxrungtham K, Puthanakit T; Predict Study Group.

Quality of life (QOL) is an important antiretroviral treatment (ART) outcome. We compared QOL among **299 Thai and Cambodian children ages 1-12 years-old, CD4 15-24% randomized to early (ART at week 0, N=149) versus deferred groups (ART when at CD4 <15%, N=150)** and also compared with QOL data from age-matched healthy controls (N=275). Primary caregivers completed PACTG QOL questionnaires at week 0 and every 24 weeks until 144 weeks. Children were enrolled during March 2006 to September 2008. Mean (SD) age of children was 6.3 (2.8) years, 58% were female, 60% were Thai, %CDC N:A:B:C was 2:62:36:0%. **During 144 weeks, all children in the early-group and 69 (46%) of deferred-group children started ART.** There was no significant difference of QOL scores between treatment groups at baseline (all p>0.05) and at week 144 (all p>0.05). **By multivariate analysis, the early-group had higher QOL score changes in five domains, including health perception (p=0.04), physical resilience (p=0.02), psychosocial well-being (p=0.04), social and role functioning (p<0.01), and symptoms (p=0.01) compared to the deferred group.** QOL of HIV-infected children in both groups were lower than healthy control in all 7 domains at baseline (all p<0.05) and 5 of 7 domains at weeks 144 (p<0.01). In conclusion, no significant difference of QOL scores between treatment groups. Early ART commencement associated with greater increase of QOL scores over 144 weeks. QOL scores in HIV-infected children were lower than healthy controls.

AIDS Res Treat. 2014;2014:675739. doi: 10.1155/2014/675739. Epub 2014 Apr 3.

Engagement with Care, Substance Use, and Adherence to Therapy in HIV/AIDS.

Nicholas PK, Willard S, Thompson C, Dawson-Rose C, Corless IB, Wantland DJ, Sefcik EF, Nokes KM, Kirksey KM, Hamilton MJ[1], Holzemer WL, Portillo CJ, Rivero Mendez M[1], Robinson LM, Rosa M, Human SP, Cuca Y, Huang E, Maryland M, Arudo J, Eller LS, Stanton MA, Driscoll M, Voss JG, Moezzi S.

Engagement with care for those living with HIV is aimed at establishing a strong relationship between patients and their health care provider and is often associated with greater adherence to therapy and treatment (Flickinger, Saha, Moore, and Beach, 2013). Substance use behaviors are linked with lower rates of engagement with care and medication adherence (Horvath, Carrico, Simoni, Boyer, Amico, and Petroli, 2013). This study is a secondary data analysis using a cross-sectional design from a larger randomized controlled trial (n = 775) that investigated the efficacy of a self-care symptom management manual for participants living with HIV. Participants were recruited from countries of Africa and the US. This study provides evidence that substance use is linked with lower self-reported engagement with care and adherence to therapy. Data on substance use and engagement are presented. Clinical implications of the study address the importance of utilizing health care system and policy factors to improve engagement with care.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24800065/

J Acquir Immune Defic Syndr. 2014 May 4. [Epub ahead of print]

Immunologic effect of zinc supplementation in HIV infected children receiving highly active antiretroviral therapy: A randomized, double blind placebo controlled trial.

Lodha R, Shah N, Mohari N, Mukherjee A, Vajpayee M, Singh R, Singla M, Saini S, Bhatnagar S, Kabra S.

BACKGROUND/OBJECTIVES:
We conducted this study to assess the immunologic effect of daily 20 mg zinc supplementation for 24 weeks in HIV-infected children older than 6 months receiving highly active antiretroviral therapy.

METHODS: 52 HIV-infected children older than 6 months in whom antiretroviral therapy was initiated were randomized to receive either 20 mg of zinc or placebo for a period of 24 weeks. Children underwent clinical examination, anthropometry and laboratory evaluations: CD4 count and percent, viral load and serum zinc level at baseline, 12 and 24 weeks. The primary outcome evaluated was CD4% value at the end of 12 weeks and 24 weeks of study intervention in children enrolled.

RESULTS: Of 52 children enrolled, 49 completed the study. The median CD4% value rose from 10% to 23% at 12 weeks and to 24.5% at 24 weeks in the zinc group, while in the placebo group, the value rose from 11% to 20% at 12 weeks and to 22% at 24 weeks (p= 0.188 for comparison between the zinc and the placebo group at 12 weeks and p= 0.3 for comparison at

24 weeks). The median (IQR) log reductions in the viral load at 12 weeks in the two arms were similar at 12 (p=0.84) and 24 weeks(p= 0.43).

CONCLUSIONS: **Supplementation of 20 mg zinc daily for 24 weeks did not have any statistically significant effect on the increase in CD4%, decrease in viral load, anthropometric indices and morbidity profile in HIV-infected children started on antiretroviral therapy**.

Management of HIV-related conditions

N Engl J Med. 2014 Jan 2;370(1):41-53. doi: 10.1056/NEJMoa1214901.

A randomized trial of prolonged co-trimoxazole in HIV-infected children in Africa.

Bwakura-Dangarembizi M, Kendall L, Bakeera-Kitaka S, Nahirya-Ntege P, Keishanyu R, Nathoo K, Spyer MJ, Kekitiinwa A, Lutaakome J, Mhute T, Kasirye P, Munderi P, Musiime V, Gibb DM, Walker AS, Prendergast AJ; Antiretroviral Research for Watoto (ARROW) Trial Team.

BACKGROUND: Co-trimoxazole (fixed-dose trimethoprim-sulfamethoxazole) prophylaxis administered before antiretroviral therapy (ART) reduces morbidity in children infected with the human immunodeficiency virus (HIV). We investigated whether children and adolescents receiving long-term ART in sub-Saharan Africa could discontinue co-trimoxazole.

METHODS: We conducted a randomized, noninferiority trial of stopping versus continuing daily open-label co-trimoxazole in children and adolescents in Uganda and Zimbabwe. Eligible participants were older than 3 years of age, had been receiving ART for more than 96 weeks, were using insecticide-treated bed nets (in malaria-endemic areas), and had not had Pneumocystis jirovecii pneumonia. Coprimary end points were hospitalization or death and adverse events of grade 3 or 4.

RESULTS:
A total of 758 participants were randomly assigned to stop or continue co-trimoxazole (382 and 376 participants, respectively), after receiving ART for a median of 2.1 years (interquartile range, 1.8 to 2.3). The median age was 7.9 years (interquartile range, 4.6 to 11.1), and the median CD4 T-cell percentage was 33% (interquartile range, 26 to 39**). Participants who stopped co-trimoxazole had higher rates of hospitalization or death than those who continued (72 participants [19%] vs. 48 [13%]; hazard ratio, 1.64; 95% confidence interval [CI], 1.14 to 2.37; P = 0.007; noninferiority not shown).** There was no evidence of variation across ages (P=0.93 for interaction). A total of 2 participants in the prophylaxis-stopped group (1%) died, as did 3 in the prophylaxis-continued group (1%). **Most hospitalizations in the prophylaxis-stopped group were for malaria (49 events, vs. 21 in the prophylaxis-continued group) or infections other than malaria (53 vs. 25), particularly pneumonia, sepsis, and meningitis.** Rates of adverse events of grade 3 or 4 were similar in the two groups (hazard ratio, 1.20; 95% CI, 0.83 to 1.72; P=0.33), but more grade 4 adverse events

occurred in the prophylaxis-stopped group (hazard ratio, 2.04; 95% CI, 0.99 to 4.22; P=0.05), with anemia accounting for the largest number of events (12, vs. 2 with continued prophylaxis).

CONCLUSIONS: **Continuing co-trimoxazole prophylaxis after 96 weeks of ART was beneficial, as compared with stopping prophylaxis, with fewer hospitalizations for both malaria and infection not related to malaria.** (Funded by the United Kingdom Medical Research Council and others; ARROW Current Controlled Trials number, ISRCTN24791884.).

Pediatr Infect Dis J. 2013 Aug;32(8):856-62. doi: 10.1097/INF.0b013e31828c3991.

Bacteremia, causative agents and antimicrobial susceptibility among HIV-1-infected children on antiretroviral therapy in Uganda and Zimbabwe.

Musiime V, Cook A, Bakeera-Kitaka S, Vhembo T, Lutakome J, Keishanyu R, Prendergast AJ, Lubwama S, Robertson V, Hughes P, Nathoo K, Munderi P, Klein N, Musoke P, Gibb DM; ARROW Trial Team.

BACKGROUND: Bacteremia is common in HIV-infected children in Africa, including after start of antiretroviral therapy (ART), but there are limited data on causative pathogens and their antimicrobial sensitivity patterns in this population.

METHODS: We analyzed data on blood cultures taken from HIV-infected children developing acute febrile illness after enrollment to the Antiretroviral Research for Watoto (ARROW) clinical trial in Uganda and Zimbabwe. Patterns of bacterial pathogens and their antimicrobial susceptibilities were determined and bacteremia rates calculated over time from ART initiation.

RESULTS: A total of 848 blood cultures were obtained from 461 children, of which 123 (14.5%) from 105 children (median age 3.5 years, 51% girls) were culture positive, including 75 (8.8%) with clearly pathogenic organisms. The event rates for positive cultures with clearly pathogenic organisms after 0-1, 2-3, 4-11 and ≥12 months on ART were 13.3, 11.4, 2.1 and 0.3 per 1000 person-months of follow-up, respectively. The pathogens isolated (n; %) were **Streptococcus pneumoniae (36; 28.3%), Staphylococcus aureus (11; 8.7%), Klebsiella pneumoniae (6; 4.7%), Pseudomonas aeruginosa (6; 4.7%), Salmonella spp (6; 4.7%), Escherichia coli (5; 3.9%), Haemophilus influenzae (1; 0.8%) and fungal spp (4; 3.1%)**. Other bacteria of doubtful pathogenicity (n = 52; 42%) were also isolated. Most isolates tested were highly (80-100%) susceptible to ceftriaxone, cefotaxime and ciprofloxacin; very few (~5%) were susceptible to cotrimoxazole; S. pneumoniae had high susceptibility to amoxicillin/ampicillin (80%).

CONCLUSIONS: **Rates of proven bacteremia were >20-fold higher immediately after starting ART compared with 12 months later in African HIV-infected children**. S. pneumoniae was most commonly isolated, suggesting need for pneumococcal vaccination and effective prophylactic antibiotics.

Cochrane Database Syst Rev. 2013 Jul 5;7:CD007545. doi: 10.1002/14651858.CD007545.pub2.

Rifamycins (rifampicin, rifabutin and rifapentine) compared to isoniazid for preventing tuberculosis in HIV-negative people at risk of active TB.

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BACKGROUND: Preventing active tuberculosis (TB) from developing in people with latent tuberculosis infection (LTBI) is important for global TB control. Isoniazid (INH) for six to nine months has 60% to 90% protective efficacy, but the treatment period is long, liver toxicity is a problem, and completion rates outside trials are only around 50%. Rifampicin or rifamycin-combination treatments are shorter and may result in higher completion rates.

OBJECTIVES: To compare the effects of rifampicin monotherapy or rifamycin-combination therapy versus INH monotherapy for preventing active TB in HIV-negative people at risk of developing active TB.

SEARCH METHODS: We searched the Cochrane Infectious Disease Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; clinical trials registries; regional databases; conference proceedings; and references, without language restrictions to December 2012; and contacted experts for relevant published, unpublished and ongoing trials.

SELECTION CRITERIA:
Randomized controlled trials (RCTs) of HIV-negative adults and children at risk of active TB treated with rifampicin, or rifamycin-combination therapy with or without INH (any dose or duration), compared with INH for six to nine months.

DATA COLLECTION AND ANALYSIS: At least two authors independently screened and selected trials, assessed risk of bias, and extracted data. We sought clarifications from trial authors. We pooled relative risks (RRs) with their 95% confidence intervals (CIs), using a random-effects model if heterogeneity was significant. We assessed overall evidence quality using the GRADE approach.

MAIN RESULTS: Ten trials are included, enrolling 10,717 adults and children, mostly HIV-negative (2% HIV-positive), with a follow-up period ranging from two to five years. Rifampicin (three/four months) vs. INH (six months). Five trials published between 1992 to 2012 compared these regimens, and one small 1992 trial in adults with silicosis did not detect a difference in the occurrence of TB over five years of follow up (one trial, 312 participants; very low quality evidence). However, more people in these trials completed the shorter course (RR 1.19, 95% CI 1.01 to 1.30; five trials, 1768 participants; moderate quality evidence). Treatment-limiting adverse events were not significantly different (four trials, 1674 participants; very low quality evidence), but rifampicin caused less hepatotoxicity (RR 0.12, 95% CI 0.05 to 0.30; four trials, 1674 participants; moderate quality evidence). Rifampicin plus INH (three months) vs. INH (six months)The 1992 silicosis trial did not detect a difference between people receiving rifampicin plus INH compared to INH alone for occurrence of active TB (one trial, 328 participants; very low quality evidence). Adherence was similar in this and a 1998 trial in people without silicosis (two trials, 524 participants; high quality evidence). No difference was detected for treatment-

limiting adverse events (two trials, 536 participants; low quality evidence), or hepatotoxicity (two trials, 536 participants; low quality evidence). Rifampicin plus pyrazinamide (two months) vs. INH (six months)Three small trials published in 1994, 2003, and 2005 compared these two regimens, and two reported a low occurrence of active TB, with no statistically significant differences between treatment regimens (two trials, 176 participants; very low quality evidence) though, apart from one child from the 1994 trial, these data on active TB were from the 2003 trial in adults with silicosis. Adherence with both regimens was low with no statistically significant differences (four trials, 700 participants; very low quality evidence). However, people receiving rifampicin plus pyrazinamide had more treatment-limiting adverse events (RR 3.61, 95% CI 1.82 to 7.19; two trials, 368 participants; high quality evidence), and hepatotoxicity (RR 4.59, 95% 2.14 to 9.85; three trials, 540 participants; moderate quality evidence). Weekly, directly-observed rifapentine plus INH (three months) vs. daily, self-administered INH (nine months)A large trial conducted from 2001 to 2008 among close contacts of TB in the USA, Canada, Brazil and Spain found directly observed weekly treatment to be non-inferior to nine months self-administered INH for the incidence of active TB (0.2% vs 0.4%, RR 0.44, 95% CI 0.18 to 1.07, one trial, 7731 participants; moderate quality evidence). The directly-observed, shorter regimen had higher treatment completion (82% vs 69%, RR 1.19, 95% CI 1.16 to 1.22, moderate quality evidence), and less hepatotoxicity (0.4% versus 2.4%; RR 0.16, 95% CI 0.10 to 0.27; high quality evidence), though treatment-limiting adverse events were more frequent (4.9% versus 3.7%; RR 1.32, 95% CI 1.07 to 1.64 moderate quality evidence)

AUTHORS' CONCLUSIONS: Trials to date of shortened prophylactic regimens using rifampicin alone have not demonstrated higher rates of active TB when compared to longer regimens with INH. Treatment completion is probably higher and adverse events may be fewer with shorter rifampicin regimens. Shortened regimens of rifampicin with INH may offer no advantage over longer INH regimens. Rifampicin combined with pyrazinamide is associated with more adverse events. A weekly regimen of rifapentine plus INH has higher completion rates, and less liver toxicity, though treatment discontinuation due to adverse events is probably more likely than with INH.

http://onlinelibrary.wiley.com/store/10.1002/14651858.CD007545.pub2/asset/CD007545.pdf?v=1&t=hxd2nwox&s=62f91f72baf0e118711d4cea8adaf3d889589a5e

Nutrition, growth and development of children with HIV

Public Health Nutr. 2013 Sep;16(9):1548-57. doi: 10.1017/S1368980013000499. Epub 2013 Mar 18.

Maternal HIV infection and other factors associated with growth outcomes of HIV-uninfected infants in Entebbe, Uganda.

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OBJECTIVE: To assess the associations between maternal HIV infection and growth outcomes of HIV-exposed but uninfected infants and to identify other predictors for poor growth among this population.

DESIGN: Within a trial of de-worming during pregnancy, the cohort of offspring was followed from birth. HIV status of the mothers and their children was investigated and growth data for children were obtained at age 1 year. Length-for-age, weight-for-age and weight-for-length Z-scores were calculated for each child; Z-scores ,22 were defined as stunting, underweight and wasting, respectively.

SETTING: The study was conducted in Entebbe municipality and Katabi subcounty, Uganda.

SUBJECTS: The sample consisted of 1502 children aged 1 year: HIV-unexposed (n 1380) and HIV-exposed not infected (n 122).

RESULTS: Prevalence of stunting, underweight and wasting was 14.2%, 8.0% and 3.9%, respectively. There was evidence for an association between maternal HIV infection and odds of being underweight (adjusted OR52.32; 95% CI 1.32, 4.09; P=0.006) but no evidence for an association with stunting or with wasting. Young maternal age, low maternal education, low birth weight, early weaning and experiencing a higher number of episodes of malaria during infancy were independent predictors for stunting and underweight. A higher number of living children in the family was associated with wasting.

CONCLUSIONS: **Maternal HIV infection was associated with being underweight in HIV-exposed uninfected infants.** The success of programmes for prevention of mother-to-child HIV transmission means that an increasing number of infants will be born to HIV-infected women without acquiring HIV. Therefore, viable nutritional interventions need to be identified for this population.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23507372/

Nutrients. 2013 Oct 11;5(10):4079-92. doi: 10.3390/nu5104079.

Impact of multi-micronutrient supplementation on growth and morbidity of HIV-infected South African children.

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Poor growth, micronutrient deficiencies and episodes of diarrhea and respiratory infections occur frequently in HIV-infected children. **We investigated whether multi-micronutrient supplementation would improve the growth performance and reduce the number of episodes of diarrhea and/or of respiratory symptoms in HIV-infected children**. In a double-blind randomized trial, **HIV-infected South African children aged 4-24 months (n = 201)**

were assigned to receive multi-micronutrient supplements or placebo daily for six months. The children were assessed for respiratory symptoms or diarrhea bi-weekly; weights and heights were measured monthly. In total, 121 children completed the six month follow up study period (60%). A total of 43 children died; 27 of them had received supplements. This difference in mortality was not statistically significant (p = 0.12). **Weight-for-height Z-scores improved significantly (p < 0.05) among children given supplements compared with those given placebo (0.40 (0.09-0.71)) versus -0.04 (-0.39-0.31) (mean (95% CI)).** Height-for-age Z-scores did not improve in both treatment groups. **The number of monthly episodes of diarrhea in the placebo group (0.36 (0.26-0.46)) was higher (p = 0.09) than in the supplement group (0.25 (0.17-0.33)) and the number of monthly episodes of respiratory symptoms was significantly higher (p < 0.05) among children on placebos (1.01 (0.83-1.79)) than those on supplements (0.66 (0.52-0.80)).** Multi-micronutrient supplements significantly improved wasting and reduced the number of episodes of diarrhea and respiratory symptoms.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24152748/

J Int AIDS Soc. 2013 Aug 13;16(1):18022. doi: 10.7448/IAS.16.1.18022.

Multivitamin supplementation improves haematologic status in children born to HIV-positive women in Tanzania.

Liu E[1], Duggan C, Manji KP, Kupka R, Aboud S, Bosch RJ, Kisenge RR, Okuma J, Fawzi WW.

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INTRODUCTION: Anaemia is prevalent among children born to HIV-positive women, and it is associated with adverse effects on cognitive and motor development, growth, and increased risks of morbidity and mortality.

OBJECTIVE:
To examine the effect of daily multivitamin supplementation on haematologic status and mother-to-child transmission (MTCT) of HIV through breastfeeding.

METHODS: A total of 2387 infants born to HIV-positive women from Dar es Salaam, Tanzania were enrolled in a randomized, double-blind, placebo-controlled trial, and provided a **daily oral supplement of multivitamins (vitamin B complex, C and E) or placebo at age 6 weeks for 24 months**. Among them, 2008 infants provided blood samples and had haemoglobin concentrations measured at baseline and during a follow-up period. Anaemia was defined as haemoglobin concentrations <11 g/dL and severe anaemia <8.5 g/dL.

RESULTS: Haemoglobin concentrations among children in the treatment group were significantly higher than those in the placebo group at 12 (9.77 vs. 9.64 g/dL, p=0.03), 18 (9.76 vs. 9.57 g/dL, p=0.004), and 24 months (9.93 vs. 9.75 g/dL, p=0.02) of follow-up. **Compared to those in the placebo group, children in the treatment group had a 12% lower risk of anaemia (hazard ratio (HR): 0.88; 95% CI: 0.79-0.99; p=0.03).** The treatment was associated with a 28% reduced risk of severe anaemia among children born to women without anaemia

(HR: 0.72; 95% CI: 0.56-0.92; p=0.008), but not among those born to women with anaemia (HR: 1.10; 95% CI: 0.79-1.54; p=0.57; p for interaction=0.007). One thousand seven hundred fifty three infants who tested HIV-negative at baseline and had HIV testing during follow-up were included in the analysis for MTCT of HIV. No association was found between multivitamin supplements and MTCT of HIV.

CONCLUSIONS: **Multivitamin supplements improve haematologic status among children born to HIV-positive women**. Further trials focusing on anaemia among HIV-exposed children are warranted in the context of antiretroviral therapy.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23948440/

J Pediatr. 2013 Nov;163(5):1409-16.e1-5. doi: 10.1016/j.jpeds.2013.06.055. Epub 2013 Aug 16.

A year-long caregiver training program improves cognition in preschool Ugandan children with human immunodeficiency virus.

Boivin MJ[1], Bangirana P, Nakasujja N, Page CF, Shohet C, Givon D, Bass JK, Opoka RO, Klein PS.

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OBJECTIVE: To evaluate mediational intervention for sensitizing caregivers (MISC). MISC biweekly caregiver training significantly enhanced child development compared with biweekly training on health and nutrition (active control) and to evaluate whether MISC training improved the emotional well-being of the caregivers compared with controls.

STUDY DESIGN: **Sixty of 120 rural Ugandan preschool child/caregiver dyads with HIV were assigned by randomized clusters to biweekly MISC training, alternating between home and clinic for 1 year.** Control dyads received a health and nutrition curriculum. Children were evaluated at baseline, 6 months, and 1 year with the Mullen Early Learning Scales and the Color-Object Association Test for memory. Caldwell Home Observation for Measurement of the Environment and videotaped child/caregiver MISC interactions also were evaluated. Caregivers were evaluated for depression and anxiety with the Hopkins Symptoms Checklist.

RESULTS: Between-group repeated-measures ANCOVA comparisons were made with age, sex, CD4 levels, viral load, material socioeconomic status, physical development, and highly active anti-retroviral therapy treatment status as covariates. The children given MISC had significantly greater gains compared with controls on the Mullen Visual Reception scale (visual-spatial memory) and on Color-Object Association Test memory. MISC caregivers significantly improved on Caldwell Home Observation for Measurement of the Environment scale and total frequency of MISC videotaped interactions. MISC caregivers also were less depressed. Mortality was less for children given MISC compared with controls during the training year.

CONCLUSIONS: MISC was effective in teaching Ugandan caregivers to enhance their children's cognitive development through practical and sustainable techniques applied during daily interactions in the home.

Prevention of parent to child transmission

J Acquir Immune Defic Syndr. 2014 Mar 1;65(3):366-74. doi: 10.1097/QAI.0000000000000052.

Efficacy and safety of an extended nevirapine regimen in infants of breastfeeding mothers with HIV-1 infection for prevention of HIV-1 transmission (HPTN 046): 18-month results of a randomized, double-blind, placebo-controlled trial.

Fowler MG, Coovadia H, Herron CM, Maldonado Y, Chipato T, Moodley D, Musoke P, Aizire J, Manji K, Stranix-Chibanda L, Fawzi W, Chetty V, Msweli L, Kisenge R, Brown E, Mwatha A, Eshleman SH, Richardson P, Allen M, George K, Andrew P, Zwerski S, Mofenson LM, Jackson JB; HPTN 046 Protocol Team.

BACKGROUND:
HPTN 046 compared the efficacy and safety of infant nevirapine (NVP) among HIV-exposed breastfed infants randomized at 6 weeks to 6 months to t NVP or placebo to prevent postnatal infection: we report final 18-month outcomes.

METHODS:
Randomized, placebo-controlled trial in 4 African countries. Infant diagnostic HIV testing was performed regularly from birth through 18 months. Kaplan-Meier analysis was used to assess 18-month cumulative infant HIV infection, HIV infection/or death, and mortality rates.

RESULTS: **Between 6 weeks and 6 months, postnatal HIV infection rates were significantly lower among infants receiving daily NVP from 6 weeks to 6 months 1.1% [95% confidence interval (CI): 0.2% to 1.8%], compared with placebo 2.4% (95% CI: 1.3% to 2.6%), P = 0.049, but not significantly lower thereafter**. Eighteen-month postnatal infection rates were low: 2.2% (95% CI: 1.1% to 3.3%) versus 3.1% (95% CI: 1.9% to 4.4%), respectively, P = 0.28. Mortality and HIV infection/death did not differ between arms at any age. Infants of women receiving antiretroviral therapy (ART) for their own health had the lowest 18-month postnatal infection rates (0.5%, 95% CI: 0.0% to 1.1%). However, HIV infection/death rates at 18 months were not significantly different for infants of mothers on ART (3.7%, 95% CI: 1.9% to 5.5%), and infants of mothers with CD4 counts of ≥ 350 cells per cubic millimeter not receiving ART (4.8%, 95% CI: 2.7% to 6.8%; P = 0.46). There were no differences in adverse events between study arms.

CONCLUSIONS: **This trial demonstrated early but not late differences in postnatal HIV transmission among infants randomized at age 6 weeks to extended NVP or placebo, underscoring the importance of continued prophylaxis throughout breastfeeding.**

AIDS. 2013 Jul 31;27(12):1911-20.

HIV transmission and 24-month survival in a randomized trial of HAART to prevent MTCT during pregnancy and breastfeeding in Botswana.

Shapiro RL, Kitch D, Ogwu A, Hughes MD, Lockman S, Powis K, Souda S, Moffat C, Moyo S, McIntosh K, van Widenfelt E, Zwerski S, Mazhani L, Makhema J, Essex M.

OBJECTIVES: HAART for prevention of mother-to-child HIV transmission (MTCT) may impact long-term survival of women and children.

DESIGN:
Randomized clinical trial.

METHODS: **HIV-infected pregnant women with CD4+ cell count at least 200 cells/µl were randomly assigned to abacavir, zidovudine, lamivudine (arm A) or lopinavir–ritonavir, zidovudine–lamivudine (arm B) from week 26 to 34 gestation through planned weaning by 6 months postpartum.** Women with baseline CD4+ cell count less than 200 cells/µl received nevirapine–zidovudine–lamivudine indefinitely (Obs arm), as did randomized women later qualifying for treatment.

RESULTS: Among 560 randomized and 170 observational women enrolled, there were 14 deaths (1.9%) – one antenatally (Obs), three from delivery to 6 months postpartum (1 arm A, 2 Obs), and 10 from 6 to 24 months postpartum (5 arm A, 3 arm B, 2 Obs). Time to death or CD4+ cell count below 200 cells/µl was shorter in arm A vs. B (P = 0.03). Of the 709 live-born children, 97% breastfed for a median of 5.8 months. Of 37 (5.2%) deaths by 24 months, nine were before breastfeeding initiated (3 arm A, 2 arm B, 4 Obs); six while breastfeeding (1 arm A, 2 arm B, 3 Obs); and 22 after weaning (9 arm A, 11 arm B, 2 Obs). Only eight children (1.1%) were HIV-infected at 24 months (6 arm A, 1 arm B, 1 Obs), all before 6 months.

CONCLUSION: **Low MTCT was maintained through extended follow-up in all arms.** Disease progression appeared slower after discontinuing protease inhibitor-based HAART, but a concerning number of maternal deaths occurred after stopping either regimen. Strategies to improve maternal and child survival in the postintervention period are required.

AIDS Behav. 2014 Apr;18(4):706-15. doi: 10.1007/s10461-014-0694-2.

Pregnant women living with HIV (WLH) supported at clinics by peer WLH: a cluster randomized controlled trial.

Richter L, Rotheram-Borus MJ, Van Heerden A, Stein A, Tomlinson M, Harwood JM, Rochat T, Van Rooyen H, Comulada WS, Tang Z.

Throughout Africa, Peer Mentors who are women living with HIV (WLH) are supporting pregnant WLH at antenatal and primary healthcare clinics (McColl in BMJ 344:e1590, 2012). We evaluate a program using this intervention strategy at 1.5 months post-birth. In a cluster randomized controlled trial in KwaZulu-Natal, South Africa, **eight clinics were randomized for their WLH to receive either: standard care (SC), based on national guidelines to prevent mother-to-child transmission (4 clinics; n = 656 WLH); or an enhanced intervention (EI; 4 clinics; n = 544 WLH). The EI consisted of four antenatal and four postnatal small group sessions led by Peer Mentors,** in addition to SC. WLH were recruited during pregnancy and 70 % were reassessed at 1.5 months post-birth. EI's effect was ascertained

on 16 measures of maternal and infant well-being using random effects regressions to control for clinic clustering. A binomial test for correlated outcomes evaluated EI's overall effectiveness. Among EI WLH reassessed, 87 % attended at least one intervention session (mean 4.1, SD 2.0). Significant overall benefits were found in EI compared to SC using the binomial test. However, it is important to note that EI WLH were significantly less likely to adhere to ARV during pregnancy compared to SC. **Secondarily, compared to SC, EI WLH were more likely to ask partners to test for HIV, better protected their infants from HIV transmission, and were less likely to have depressed mood and stunted infants.** Adherence to clinic intervention groups was low, yet, there were benefits for maternal and infant health at 1.5 months post-birth.

PLoS One. 2014 Jan 22;9(1):e84867. doi: 10.1371/journal.pone.0084867. eCollection 2014.

A cluster randomized controlled trial evaluating the efficacy of peer mentors to support South African women living with HIV and their infants.

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OBJECTIVE: We evaluate the effect of clinic-based support by HIV-positive Peer Mentors, in addition to standard clinic care, on maternal and infant well-being among Women Living with HIV (WLH) from pregnancy through the infant's first year of life.

METHODS: In a cluster randomized controlled trial in KwaZulu-Natal, South Africa, eight clinics were randomized for pregnant WLH to receive either: a Standard Care condition (SC; 4 clinics; n=656 WLH); or an Enhanced Intervention (EI; 4 clinics; n=544 WLH). WLH in the EI were invited to attend four antenatal and four postnatal meetings led by HIV-positive Peer Mentors, in addition to SC. WLH were recruited during pregnancy, and at least two post-birth assessment interviews were completed by 57% of WLH at 1.5, 6 or 12 months. EI's effect was ascertained on 19 measures of maternal and infant well-being using random effects regressions to control for clinic clustering. A binomial test for correlated outcomes evaluated EI's overall efficacy.

FINDINGS: WLH attended an average of 4.1 sessions (SD=2.0); 13% did not attend any sessions. **Significant overall benefits were found in EI compared to SC using the binomial test. Secondarily, over time, WLH in the EI reported significantly fewer depressive symptoms and fewer underweight infants than WLH in the SC condition**. EI WLH were significantly more likely to use one feeding method for six months and exclusively breastfeed their infants for at least 6 months.

CONCLUSIONS: WLH benefit by support from HIV-positive Peer Mentors, even though EI participation was partial, with incomplete follow-up rates from 6-12 months.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24465444/

Comment
The above 2 papers look nearly identical; same location, same number of women with HIV enrolled, same outcomes, published just a few months apart in different journals.

J Int AIDS Soc. 2013 Dec 20;16:18865. doi: 10.7448/IAS.16.1.18865.

Effects of postnatal interventions for the reduction of vertical HIV transmission on infant growth and non-HIV infections: a systematic review.

Zunza M, Mercer GD, Thabane L, Esser M, Cotton MF.

INTRODUCTION: Guidelines in resource-poor settings have progressively included interventions to reduce postnatal HIV transmission through breast milk. In addition to HIV-free survival, infant growth and non-HIV infections should be considered. Determining the effect of these interventions on infant growth and non-HIV infections will inform healthcare decisions about feeding HIV-exposed infants. We synthesize findings from studies comparing breast to formula feeding, early weaning to standard-duration breastfeeding, breastfeeding with extended antiretroviral (ARV) to short-course ARV prophylaxis, and alternative preparations of infant formula to standard formula in HIV-exposed infants, focusing on infant growth and non-HIV infectious morbidity outcomes. The review objectives were to collate and appraise evidence of interventions to reduce postnatal vertical HIV transmission, and to estimate their effect on growth and non-HIV infections from birth to two years of age among HIV-exposed infants.

METHODS: We searched PubMed, SCOPUS, and Cochrane CENTRAL Controlled Trials Register. We included randomized trials and prospective cohort studies. Two authors independently extracted data and evaluated risk of bias. Rate ratios and mean differences were used as effect measures for dichotomous and continuous outcomes, respectively. Where pooling was possible, we used fixed-effects meta-analysis to pool results across studies. Quality of evidence was assessed using the GRADE approach.

RESULTS AND DISCUSSION: **Prospective cohort studies comparing breast- versus formula-fed HIV-exposed infants found breastfeeding to be protective against diarrhoea in early life [risk ratio (RR)=0.31; 95% confidence interval (CI)=0.13 to 0.74]. The effect of breastfeeding against diarrhoea [hazard ratio (HR)=0.74; 95% CI=0.57 to 0.97] and respiratory infections (HR=0.65; 95% CI=0.41 to 1.00) was significant through two years of age.** The only randomized controlled trial (RCT) available showed that breastfeeding tended to be protective against malnutrition (RR=0.63; 95% CI=0.36 to 1.12). We found no statistically significant differences in the rates of non-HIV infections or malnutrition between breast-fed infants in the extended and short-course ARV prophylaxis groups.

CONCLUSIONS: Low to moderate quality evidence suggests breastfeeding may improve growth and non-HIV infection outcomes of HIV-exposed infants. Extended ARV prophylaxis

does not appear to increase the risk for HIV-exposed infants for adverse growth or non-HIV infections compared to short-course ARV prophylaxis.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24369738/

Trop Med Int Health. 2014 Mar;19(3):256-66. doi: 10.1111/tmi.12257. Epub 2014 Jan 17.

Goodstart: a cluster randomised effectiveness trial of an integrated, community-based package for maternal and newborn care, with prevention of mother-to-child transmission of HIV in a South African township.

Tomlinson M[1], Doherty T, Ijumba P, Jackson D, Lawn J, Persson LÅ, Lombard C, Sanders D, Daviaud E, Nkonki L, Goga A, Rohde S, Sitrin D, Colvin M, Chopra M.

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BACKGROUND: Progress towards MDG4 for child survival in South Africa requires effective prevention of mother-to-child transmission (PMTCT) of HIV including increasing exclusive breastfeeding, as well as a new focus on reducing neonatal deaths. This necessitates increased focus on the pregnancy and early post-natal periods, developing and scaling up appropriate models of community-based care, especially to reach the peri-urban poor.

METHODS: **We used a randomised controlled trial with 30 clusters (15 in each arm) to evaluate an integrated, scalable package providing two pregnancy visits and five post-natal home visits delivered by community health workers in Umlazi, Durban, South Africa.** Primary outcomes were exclusive and appropriate infant feeding at 12 weeks post-natally and HIV-free infant survival.

RESULTS: **At 12 weeks of infant age, the intervention was effective in almost doubling the rate of exclusive breastfeeding (risk ratio 1.92; 95% CI: 1.59-2.33) and increasing infant weight and length-for-age z-scores (weight difference 0.09; 95% CI: 0.00-0.18, length difference 0.11; 95% CI: 0.03-0.19).** No difference was seen between study arms in HIV-free survival. Women in the intervention arm were also more likely to take their infant to the clinic within the first week of life (risk ratio 1.10; 95% CI: 1.04-1.18).

CONCLUSIONS: The trial coincided with national scale up of ARVs for PMTCT, and this could have diluted the effect of the intervention on HIV-free survival. **We have demonstrated that implementation of a pro-poor integrated PMTCT and maternal, neonatal and child health home visiting model is feasible and effective.** This trial could inform national primary healthcare reengineering strategies in favour of home visits. The dose effect on exclusive breastfeeding is notable as improving exclusive breastfeeding has been resistant to change in other studies targeting urban poor families.

J Acquir Immune Defic Syndr. 2013 Aug 15;63(5):578-84. doi: 10.1097/QAI.0b013e31829c48ad.

Hair and plasma data show that lopinavir, ritonavir, and efavirenz all transfer from mother to infant in utero, but only efavirenz transfers via breastfeeding.

Gandhi M[1], Mwesigwa J, Aweeka F, Plenty A, Charlebois E, Ruel TD, Huang Y, Clark T, Ades V, Natureeba P, Luwedde FA, Achan J, Kamya MR, Havlir DV, Cohan D; Prevention of Malaria and HIV disease in Tororo (PROMOTE) study.

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BACKGROUND: As efforts intensify to eliminate perinatal HIV transmission, understanding kinetics of maternal-to-child transfer of antiretrovirals during pregnancy and breastfeeding is critical. Antiretroviral levels in plasma, cord blood, and breastmilk reflect exposure over short intervals. Hair concentrations reflect cumulative exposure and can uniquely quantify in utero transfer of maternal medications to infants. We measured plasma and hair antiretroviral levels in HIV-infected Ugandan mothers and their infants at delivery and during breastfeeding to assess transfer.

METHODS: HIV-infected pregnant women were randomized to lopinavir/ritonavir- or efavirenz-based therapy in a larger trial (the Prevention of Malaria and HIV disease in Tororo, PROMOTE). At 0, 8, and 12 weeks postpartum, plasma antiretroviral levels were measured in 117 mother-infant pairs; hair levels were assayed at 12 weeks. Ratios and correlations of infant:maternal concentrations were calculated.

RESULTS: By 12 weeks, 90.4% of mothers reported exclusive breastfeeding. **Hair and plasma levels over time suggest moderate (47%) to extensive (87%) in utero transfer of lopinavir and ritonavir, respectively, but negligible transfer of either via breastfeeding.** Moderate transfer of efavirenz occurs during pregnancy and breastfeeding (40% cumulative; 15% during breastfeeding). Despite differences in exposure, no infant seroconversions or correlations between infant hair/plasma antiretroviral levels and adverse effects were observed.

CONCLUSIONS: Using a unique approach combining hair and plasma data, we found that different antiretrovirals have distinct kinetics of mother-to-infant transfer. Efavirenz transfers during both pregnancy and breastfeeding, whereas lopinavir and ritonavir transfer only in utero. Further study of the degree and timing of maternal-to-child transfer by antiretroviral will help optimize strategies that protect infants and minimize toxicities during periods of risk.

J Antimicrob Chemother. 2013 Nov;68(11):2609-15. doi: 10.1093/jac/dkt246. Epub 2013 Jul 17.

Effect of 7 days of phenytoin on the pharmacokinetics of and the development of resistance to single-dose nevirapine for perinatal HIV prevention: a randomized pilot trial.

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OBJECTIVES: To confirm whether 7 days of phenytoin, an enzyme inducer, would decrease the elimination half-life of single-dose nevirapine and to investigate its effect on the development of nevirapine resistance in pregnant, HIV-infected women.

METHODS: In a pharmacokinetic pilot trial (NCT01187719), HIV-infected, antiretroviral (ARV)-naive pregnant women ≥18 years old from Zambia and Tanzania and with CD4 cell counts >350 cells/mm(3) were randomized 1 : 1 to a control (zidovudine pre-delivery, single-dose nevirapine/zidovudine/lamivudine at delivery and zidovudine/lamivudine for 7 days post-delivery) or an intervention (control plus 184 mg of phenytoin once daily for 7 days post-delivery) group. Primary endpoints were the pharmacokinetics of and resistance to nevirapine.

RESULTS: Thirty-five and 37 women were allocated to the control and intervention groups, with median (IQR) ages of 27 (23-31) and 27 (23-33) years, respectively. Twenty-three and 23 women had detectable nevirapine levels at delivery and subsequent samples in the control and the intervention groups, respectively. Geometric mean (GM) (95% CI) plasma levels of nevirapine at delivery were 1.02 (0.58-1.78) mg/L and 1.14 (0.70-1.86) mg/L in the control and intervention groups, respectively (P = 0.76). One week after delivery, 0/23 (0%) and 15/22 (68%) control and intervention mothers, respectively, had undetectable levels of nevirapine (<0.05 mg/L; P<0.001). One week later, the figures were 10/21 (48%) and 18/19 (95%) mothers, respectively (P = 0.002). The GM (95% CI) half-life of nevirapine was 63.2 (52.8-75.7) versus 25.5 (21.6-30.1) h in the control group versus the intervention group (P < 0.001). New nevirapine mutations were found in 0/20 (0%) intervention-group mothers versus 1/21 (5%) control-group mothers. Overall, there was no difference in adverse events reported between the control and intervention arms (P > 0.28).

CONCLUSIONS: Adding 7 days of an enzyme inducer to single-dose nevirapine to prevent mother-to-child transmission of HIV significantly reduced subtherapeutic nevirapine levels by shortening the half-life of nevirapine. As prolonged subtherapeutic nevirapine dosage leads to the emergence of resistance, single-dose nevirapine could be used with phenytoin as an alternative if other ARVs were unavailable.

J Acquir Immune Defic Syndr. 2013 Aug 15;63(5):572-7. doi: 10.1097/QAI.0b013e31829308f8.

No clinically significant drug-resistance mutations in HIV-1 subtype C-infected women after discontinuation of NRTI-based or PI-based HAART for PMTCT in Botswana.

Souda S[1], Gaseitsiwe S, Georgette N, Powis K, Moremedi D, Iketleng T, Leidner J, Moffat C, Ogwu A, Lockman S, Moyo S, Mmalane M, Musonda R, Makhema J, Essex M, Shapiro R.

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Risk of developing drug resistance after stopping antiretroviral regimens to prevent mother-to-child HIV-1 transmission is unknown. The Mma Bana Study randomized treatment-naive pregnant women with CD4 ≥200 cells per cubic millimeter to receive either abacavir/zidovudine/lamivudine [triple nucleoside reverse transcriptase inhibitor (NRTI) arm] or lopinavir/ritonavir/zidovudine/lamivudine [protease inhibitor (PI) arm]. Drugs were discontinued after 6 months of breastfeeding. One month after discontinuation, 29 NRTI arm samples and 25 PI arm samples were successfully genotyped. No clinically significant antiretroviral resistance mutations were detected. Eight minor resistance mutations were found among 11 (20%) women (3 from NRTI arm and 8 from PI arm), occurring at similar frequencies to those reported in HIV-1 subtype C treatment-naive cohorts.

Contemp Clin Trials. 2013 Sep;36(1):187-97. doi: 10.1016/j.cct.2013.06.013. Epub 2013 Jun 29.

Optimizing PMTCT service delivery in rural North-Central Nigeria: protocol and design for a cluster randomized study.

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Nigeria has more HIV-infected women who do not receive needed services for the prevention of mother-to-child transmission of HIV (PMTCT) than any other nation in the world. To meet the UNAIDS/WHO goal of eliminating mother-to-child HIV transmission by 2015, multiple interventions will be required to scale up PMTCT services, especially to lower-level, rural health facilities. To address this, we are conducting a cluster-randomized controlled study to evaluate the impact and cost-effectiveness of a novel, family-focused integrated package of PMTCT services. A systematic re-assignment of patient care responsibilities coupled with the adoption of point-of-care CD4 + cell count testing could facilitate the ability of lower-cadre health providers to manage PMTCT care, including the provision and scale-up of antiretroviral therapy (ART) to pregnant women in rural settings. Additionally, as influential community members, male partners could support their partners' uptake of and adherence to PMTCT care. We describe an innovative approach to scaling up PMTCT service provision that incorporates considerations of where and from whom women can access services (task-shifting), ease of obtaining a CD4 + cell count result (point-of-care testing), the degree of HIV service integration for HIV-infected women and their infants, and the level of family and community involvement (specifically male partner involvement). This systematic approach, if proven feasible and effective, could be scaled up in Nigeria and similar resource-limited settings as a means to accelerate progress toward eliminating mother-to-child transmission of HIV and help women with HIV infection take ART and live long, healthy lives (Trial registration: NCT01805752).

J Acquir Immune Defic Syndr. 2013 Aug 1;63(4):e125-32. doi: 10.1097/QAI.0b013e3182987ce6.

Noninferiority of a task-shifting HIV care and treatment model using peer counselors and nurses among Ugandan women initiated on ART: evidence from a randomized trial.

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OBJECTIVE: To assess the noninferiority of a task-shifting HIV treatment model relying on peer counselors and nurses compared with a physician-centered model among HIV-1-positive women initiated on antiretroviral therapy (ART) at a prevention of mother-to-child transmission clinic in Mulago Hospital, Uganda.

METHODS: **HIV-1-infected ART eligible naive women were randomized to either nurse-peer (intervention) or doctor-counselor (standard model) arm.** The primary endpoint was virologic success defined attaining a viral load < 400 RNA copies per milliliter 6-12 months after ART initiation. Noninferiority was defined as the lower 95% confidence limit for the difference in proportions with virologic success being less than 10%. Secondary outcomes included immunologic success (mean CD4 count increase from baseline) and pill count.

RESULTS: Data on 85 participants were analyzed (n = 45 in the intervention and n = 40 in the standard model). **The proportion of participants with virologic success was similar in the standard and intervention models [91% versus 88% respectively; difference, 3%; 95% confidence interval (CI): -11% to 12%].** Probability of viral detection at 6-12 months' time point was similar in the 2 models (log-rank test P = 0.73). Immunologic and pill count indicators were also similar in the intervention and standard models, with mean CD4 increase of 217 versus 206 cells per microliter (difference, 11; 95% CI: -60 to 82 cells/μL) and pill counts of 99.8% versus 99.7% (difference, 0.0; 95% CI: -5% to 5%) respectively.

CONCLUSIONS: **Nurses and peer counselors were not inferior in providing ART follow-up care to postpartum women, an approach that may help deliver treatment to many more HIV-infected people.**

HIV vaccine

J Acquir Immune Defic Syndr. 2014 Mar 1;65(3):268-77. doi: 10.1097/01.qai.0000435600.65845.31.

Immunogenicity of ALVAC-HIV vCP1521 in infants of HIV-1-infected women in Uganda (HPTN 027): the first pediatric HIV vaccine trial in Africa.

Kaleebu P[1], Njai HF, Wang L, Jones N, Ssewanyana I, Richardson P, Kintu K, Emel L, Musoke P, Fowler MG, Ou SS, Jackson JB, Guay L, Andrew P, Baglyos L, Cao H; HPTN 027 protocol team.

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Center, Kampala, Uganda; ||Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD; ¶Makerere University-Johns Hopkins University Research Collaboration, Kampala, Uganda; #Department of Paediatrics and Child Health, College of Health Sciences, Makerere University, Kampala, Uganda; **George Washington University School of Public Health and Health Services, Washington, DC; ††FHI 360, Durham, NC; and ‡‡Sanofi Pasteur, Discovery Drive, Swiftwater, PA.

OBJECTIVE: Maternal-to-child-transmission of HIV-1 infection remains a significant cause of HIV-1 infection despite successful prevention strategies. Testing protective HIV-1 vaccines remains a critical priority. **The immunogenicity of ALVAC-HIV vCP1521 (ALVAC) in infants born to HIV-1-infected women in Uganda was evaluated in the first pediatric HIV-1 vaccine study in Africa.**

DESIGN: **HIV Prevention Trials Network 027 was a randomized, double-blind, placebo-controlled phase I trial to evaluate the safety and immunogenicity of ALVAC in 60 infants born to HIV-1-infected mothers with CD4 counts of >500 cells per microliter, which were randomized to the ALVAC vaccine or placebo**. ALVAC-HIV vCP1521 is an attenuated recombinant canarypox virus expressing HIV-1 clade E env, clade B gag, and protease gene products.

METHODS: Infants were vaccinated at birth and 4, 8, and 12 weeks of age with ALVAC or placebo. Cellular and humoral immune responses were evaluated using interferon-γ enzyme-linked immunosorbent spot, carboxyfluorescein diacetate succinimidyl ester proliferation, intracellular cytokine staining, and binding and neutralizing antibody assays. Fisher exact test was used to compare positive responses between the study arms.

RESULTS: **Low levels of antigen-specific CD4 and CD8 T-cell responses (intracellular cytokine assay) were detected at 24 months (CD4-6/36 vaccine vs. 1/9 placebo; CD8-5/36 vaccine vs. 0/9 placebo) of age.** There was a nonsignificant trend toward higher cellular immune response rates in vaccine recipients compared with placebo. There were minimal binding antibody responses and no neutralizing antibodies detected.

CONCLUSIONS: **HIV-1-exposed infants are capable of generating low levels of cellular immune responses to ALVAC vaccine, similar to responses seen in adults.**

Integrated approaches to HIV prevention

J Acquir Immune Defic Syndr. 2013 Jul;63 Suppl 2:S221-7. doi: 10.1097/QAI.0b013e318299c3f4.

Can combination prevention strategies reduce HIV transmission in generalized epidemic settings in Africa? The HPTN 071 (PopART) study plan in South Africa and Zambia.

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The HIV Prevention Trials Network (HPTN) is conducting the HPTN 071 (PopART) study in 21 communities in Zambia and South Africa with support from a consortium of funders. **HPTN 071 (PopART) is a community-randomized trial of a combination prevention strategy to reduce HIV incidence in the context of the generalized epidemic of southern Africa.** The full PopART intervention strategy is anchored in **home-based HIV testing and facilitated linkage of HIV-infected persons to care through community health workers and universal antiretroviral therapy for seropositive persons regardless of CD4+ cell count or HIV viral load**. To further reduce the risk of HIV acquisition among uninfected individuals, the study aims to **expand voluntary medical male circumcision, diagnosis and treatment of sexually transmitted infections, behavioral counseling, and condom distribution**. The full PopART intervention strategy also incorporates promotion of other interventions designed to reduce HIV and tuberculosis transmission, including optimization of the **prevention of mother-to-child HIV transmission and enhanced individual and public health tuberculosis services**. Success for the PopART strategy depends on the ability to increase coverage for the study interventions whose uptake is a necessary antecedent to a prevention effect. Processes will be measured to assess the degree of penetration of the interventions into the communities. A randomly sampled population cohort from each community will be used to measure the impact of the PopART strategy on HIV incidence over 3 years. We describe the strategy being tested and progress to date in the HPTN 071 (PopART) study.

Helminth and other gastrointestinal disorders

(See also Anaemia, Diarrhoea, Micronutrients and food fortification)

S Afr Med J. 2013 Oct 23;103(12):921-4. doi: 10.7196/samj.7012.

Effectiveness of sequential v. standard triple therapy for treatment of Helicobacter pylori infection in children in Nairobi, Kenya.

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BACKGROUND: Once the diagnosis of Helicobacter pylori is confirmed, treatment requires at least two antibiotics and an acid inhibitor for a minimum of seven days. Unfortunately, treatment failures are being frequently reported. Treatment regimens that include sequential administration of antibiotics with acid inhibitors have been developed to try and increase the rate of eradication.

OBJECTIVE: **To determine the effectiveness of a novel 10-day sequential therapy compared with the standard 10-day triple therapy for treatment of H. pylori infection in children**.

METHODS: A double-blinded, randomised, controlled trial was conducted. Children under the age of 16 years with recurrent abdominal pain associated with dyspepsia and diagnosed with H. pylori by histology were randomly allocated either to a 10-day sequential treatment regimen or to a 10-day conventional triple therapy. Analysis of the outcome of this study was based on clinical improvement and confirmed H. pylori eradication based on stool H. pylori antigen detection and/or repeat endoscopy.

RESULTS: Of the 71 patients included in the analysis, 45 (63.4%) were given the 10-day conventional treatment while 26 (36.6%) received the 10-day sequential treatment. **There was no difference in clinical improvement after treatment in the two therapies. However, there was a significant difference in the eradication of H. pylori between the conventional v. sequential regimens (48.8% v. 84.6%, respectively; p=0.02, odds ratio 0.19).**

CONCLUSION: **The sequential treatment had a significantly higher H. pylori eradication rate than the conventional treatment**.

PLoS Negl Trop Dis. 2013 Oct 17;7(10):e2501. doi: 10.1371/journal.pntd.0002501. eCollection 2013.

Effect of maternal Schistosoma mansoni infection and praziquantel treatment during pregnancy on Schistosoma mansoni infection and immune responsiveness among offspring at age five years.

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INTRODUCTION: Offspring of Schistosoma mansoni-infected women in schistosomiasis-endemic areas may be sensitised in-utero. This may influence their immune responsiveness to schistosome infection and schistosomiasis-associated morbidity. Effects of praziquantel treatment of S. mansoni during pregnancy on risk of S. mansoni infection among offspring, and on their immune responsiveness when they become exposed to S. mansoni, are unknown. **Here we examined effects of praziquantel treatment of S. mansoni during pregnancy on prevalence of S. mansoni and immune responsiveness among offspring at age five years.**

METHODS: In a trial in Uganda (ISRCTN32849447, http://www.controlled-trials.com/ISRCTN32849447/elliott), offspring of women treated with praziquantel or placebo during pregnancy were examined for S. mansoni infection and for cytokine and antibody responses to SWA and SEA, as well as for T cell expression of FoxP3, at age five years.

RESULTS: **Of the 1343 children examined, 32 (2.4%) had S. mansoni infection at age five years based on a single stool sample. Infection prevalence did not differ between children of treated or untreated mothers.** Cytokine (IFNγ, IL-5, IL-10 and IL-13) and antibody (IgG1, Ig4 and IgE) responses to SWA and SEA, and FoxP3 expression, were higher

among infected than uninfected children. Praziquantel treatment of S. mansoni during pregnancy had no effect on immune responses, with the exception of IL-10 responses to SWA, which was higher in offspring of women that received praziquantel during pregnancy than those who did not.

CONCLUSION: **We found no evidence that maternal S. mansoni infection and its treatment during pregnancy influence prevalence and intensity of S. mansoni infection or effector immune response to S. mansoni infection among offspring at age five years**, but the observed effects on IL-10 responses to SWA suggest that maternal S. mansoni and its treatment during pregnancy may affect immunoregulatory responsiveness in childhood schistosomiasis. This might have implications for pathogenesis of the disease.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24147175/

Deworming

Trop Med Int Health. 2013 Aug;18(8):942-51. doi: 10.1111/tmi.12128.

Cluster-randomised trial of the impact of school-based deworming and iron supplementation on the cognitive abilities of schoolchildren in Sri Lanka's plantation sector.

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OBJECTIVE: To assess the impact of deworming and iron supplementation on the cognitive abilities and educational achievement of school-age children in Sri Lanka.

METHODS: **Prospective, placebo-controlled randomised study. The treatment group received deworming and weekly iron supplementation for 6 months; the control group received placebo for both the anthelmintic and iron**. A mixed effects regression model was used to answer the main research question. To increase the precision of this study's estimates, various background variables were controlled for that were not related to treatment but could have some impact on the outcome.

RESULTS: **The prevalence of soil-transmitted helminth (STH) infection was reduced in the treatment group (n = 615), with significant differences between treatment and control groups (n = 575) in the levels of Ascaris and Trichuris. No impact was found on haemoglobin (Hb) levels, nor any significant impact on concentration levels or on educational test scores.**

CONCLUSION: Decline in STH prevalence alone, in the absence of improved Hb status, produced no evidence of impact on concentration levels or educational test scores.

PLoS Negl Trop Dis. 2013 Sep 12;7(9):e2397. doi: 10.1371/journal.pntd.0002397. eCollection 2013.

Impact of health education on soil-transmitted helminth infections in schoolchildren of the Peruvian Amazon: a cluster-randomized controlled trial.

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BACKGROUND: To control soil-transmitted helminth (STH) infections, the World Health Organization recommends school-based deworming programs with a health hygiene education component. The effect of such health hygiene interventions, however, has not been adequately studied. The objective of the present study was to determine the effectiveness of a health hygiene education intervention on the occurrence of STH re-infection four months post-deworming.

METHODOLOGY/PRINCIPAL FINDINGS: An open-label pair-matched cluster-randomized trial was conducted in Grade 5 schoolchildren of 18 primary schools (9 intervention and 9 control) in the Peruvian Amazon. Baseline assessment included interview with a pre-tested questionnaire and collection of single stool specimens that were examined using the single Kato-Katz thick smear. **All schoolchildren were then treated with single-dose albendazole (400 mg). Schoolchildren in intervention schools then received 1) an initial one hour in-class activity on health hygiene and sanitation and 30-minute refresher activities every two weeks over four months; and 2) a half-day workshop for teachers and principals, while children in control schools did not.** Four months later, STH infection was re-assessed in all schools by laboratory technologists blinded to intervention status. From April 21-October 20, 2010, a total of **1,089 schoolchildren (518 and 571 from intervention and control schools, respectively) participated in this study**. Intervention children scored significantly higher on all aspects of a test of STH-related knowledge compared with control children (aOR = 18·4; 95% CI: 12·7 to 26·6). **The intensity of Ascaris lumbricoides infection at follow-up was statistically significantly lower (by 58%) in children in intervention schools compared with children in control schools (aIRR = 0·42; 95% CI = 0·21 to 0·85).** No significant changes in hookworm or Trichuris trichiura intensity were observed.

CONCLUSIONS/SIGNIFICANCE: A school-based health hygiene education intervention was effective in increasing STH knowledge and in reducing Ascaris lumbricoides infection. The benefits of school-based periodic deworming programs are likely to be enhanced when a sustained health hygiene education intervention is integrated into school curricula.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24069469/

Am J Trop Med Hyg. 2013 Jul;89(1):23-31. doi: 10.4269/ajtmh.13-0009. Epub 2013 May 20.

Rapid re-infection with soil-transmitted helminths after triple-dose albendazole treatment of school-aged children in Yunnan, People's Republic of China.

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Post-treatment soil-transmitted helminth re-infection patterns were studied as part of a randomized controlled trial among school-aged children from an ethnic minority group in Yunnan province, People's Republic of China. **Children with a soil-transmitted helminth infection (N = 194) were randomly assigned to triple-dose albendazole or placebo and their infection status monitored over a 6-month period** using the Kato-Katz and Baermann techniques. Baseline prevalence of Trichuris trichiura, Ascaris lumbricoides, hookworm, and Strongyloides stercoralis were 94.5%, 93.3%, 61.3%, and 3.1%, respectively, with more than half of the participants harboring triple-species infections. For the intervention group (N = 99), the 1-month post-treatment cure rates were 96.7%, 91.5%, and 19.6% for hookworm, A. lumbricoides, and T. trichiura, respectively. Egg reduction rates were above 88% for all three species. Rapid re-infection with A. lumbricoides was observed: the prevalence 4 and 6 months post-treatment was 75.8% and 83.8%, respectively. Re-infection with hookworm and T. trichiura was considerably slower.

Intravenous fluids

Indian J Pediatr. 2014 May 16. [Epub ahead of print]

Isotonic Intravenous Maintenance Fluid Reduces Hospital Acquired Hyponatremia in Young Children with Central Nervous System Infections.

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OBJECTIVE: To find the appropriate type of intravenous fluid (isotonic vs. hypotonic saline in 5 % dextrose) for empiric maintenance fluid therapy in children with central nervous system (CNS) infections that reduces the incidence of hospital acquired hyponatremia.

METHODS: This blinded randomized controlled trial included hospitalized children aged 3 mo to 5 y with suspected CNS infections requiring intravenous maintenance fluid for at least 24 h. **The subjects were randomized to receive 0.9 % saline (Group-A), 0.45 % saline (Group-B) and 0.18 % saline (Group-C) at standard maintenance rate**. The outcome measures were proportion of patients developing hyponatremia (serum sodium < 135 mmol/L) after 24 h and serum sodium values at 6, 12, 18, 24 h of receiving maintenance fluids.

RESULTS: Of the 92 patients enroled, 31, 30 and 31 patients were randomized to Group A, B and C, respectively. **Majority (60.7 %) of the patients in Group-C developed hyponatremia compared with 7.1 % of the children in Group-A and 46.1 % in Group-B.**

During first 24 h of fluid administration successive fall in the serum sodium values was observed in patients receiving hypotonic fluids. **The risk of developing hyponatremia was nearly 6½ (95 % confidence interval (CI) 1.6-26) to 8.5 (95 % CI 2.16-33.39) times more in patients who received hypotonic saline compared to those who received isotonic saline**.

CONCLUSIONS: **Administration of 0.9 % saline in 5 % dextrose as intravenous maintenance fluid in children with CNS infection leads to significantly less incidence of hyponatremia when compared to that with hypotonic fluids**.

Comment
This is an important study which will help guide WHOs IV fluid recommendations in critically ill children. There are many cases of severe neurological injury associated with severe hyponatraemia due to the use of very hypotonic fluids (such as 0.18% saline, 30mmol/L Na^+), such that 0.18% saline has been banned in several countries. This study shows that using fluids with 77 mmol/L Na^+ hyponatraemia is not uncommon. Iatrogenic hyponatraemia was avoided by using 0.9% NaCl (150 mmol/L Na+). Are there any down-sides to using a fluid based on normal saline? Potential for worsening or persistence of hyerchloraemia metabolic acidosis because of the high chloride content of 0.9% NaCl (also 150mmol/L Cl^- compared with the normal serum concentration of less than 110mmol/L. Hyperchloraemia has been associated with impaired renal perfusion and increased risk of renal failure in critically ill adults. Alternatives to avoid this include Hartmanns solution (sodium concentration 130mmol/L and chloride content 110 mmol/L).

Kidney disease

Indian Pediatr. 2013 Oct;50(10):923-8. Epub 2013 Mar 5.

Effect of enalapril on glomerular filtration rate and proteinuria in children with chronic kidney disease: a randomized controlled trial.

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OBJECTIVE: To evaluate the efficacy of enalapril treatment on decline in glomerular filtration rate and reduction in proteinuria in children with chronic kidney disease (CKD).

DESIGN: Open-label, randomized controlled trial. Setting: Pediatric nephrology clinic at a tertiary-care referral hospital.

INTERVENTION: Children with GFR between 15-60 mL/min/1.73 m2 were randomized to receive either enalapril at 0.4 mg/kg /day or no enalapril for 1 year.

OUTCOME MEASURES: Change in GFR using 99mTc-DTPA and urine protein to creatinine ratio. Secondary outcomes included occurrence of composite outcome (30% decline in GFR or end stage renal disease) and systolic and diastolic blood pressure SDS during the study period.

RESULTS: 41 children were randomized into two groups; 20 received enalapril while 21 did not receive enalapril. During 1 year, GFR decline was not different in the two groups (regression coefficient (r) 0.40, 95% CI -4.29 to 5.09, P=0.86). The mean proteinuria reduction was 65% in the enalapril group, significantly higher than control group. The difference was significant even after adjustment for blood pressure was 198.5 (CI 97.5, 299.3; P<0.001). **3 (17.6%) patients in enalapril and 7 (36.8%) in non-enalapril group attained the composite outcome.**

CONCLUSIONS: **Enalapril is effective in reducing proteinuria in children with CKD and might be renoprotective in proteinuric CKD**.

http://www.indianpediatrics.net/oct2013/923.pdf

Pediatr Nephrol. 2013 Aug;28(8):1261-6. doi: 10.1007/s00467-013-2431-x. Epub 2013 Feb 19.

Ergocalciferol decreases erythropoietin resistance in children with chronic kidney disease stage 5.

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BACKGROUND: Vitamin D insufficiency is related to erythropoietin resistance in chronic kidney disease (CKD). This study was conducted to evaluate the effect of ergocalciferol on the dose of erythrocyte-stimulating agent (ESA) administered to children with CKD stage 5 and vitamin D insufficiency.

METHODS: Twenty patients aged <18 years with CKD stages 5 or 5D and vitamin D insufficiency were divided into two groups. **During the 12-week study, ten patients received oral ergocalciferol (treatment) whereas the other ten patients did not (control).** The ESA dosage was recorded monthly.

RESULTS: There were no significant differences in demographic data, ESA dosages, and laboratory data, including corrected calcium, phosphorus, parathyroid hormone, hemoglobin, ferritin, 25-hydroxyvitamin D (25D), and transferrin saturation levels, between the two groups at baseline. **At the completion of the study, serum 25D levels in the treatment group were significantly increased from baseline (p = 0.02) and were significantly higher than the serum 25D levels in the controls (p < 0.005). The ESA dosage in the treatment group was significantly decreased when compared to baseline (p = 0.04).**

CONCLUSIONS: Vitamin D deficiency should be routinely detected and treated. Our results show that the administration of ergocalciferol in conjunction with 1,25-dihydroxyvitamin D3 reduced the dose of ESA required to treat children with CKD stages 5 and 5D and may decrease erythropoietin resistance.

Malaria

Insecticide-treated bed nets

Malar J. 2013 Oct 11;12:363. doi: 10.1186/1475-2875-12-363.

The effect of insecticide-treated bed nets on the incidence and prevalence of malaria in children in an area of unstable seasonal transmission in western Myanmar.

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BACKGROUND:
Insecticide-treated bed nets (ITN) reduce malaria morbidity and mortality consistently in Africa, but their benefits have been less consistent in Asia. This study's objective was to evaluate the malaria protective efficacy of village-wide usage of ITN in Western Myanmar and estimate the cost-effectiveness of ITN compared with extending early diagnosis and treatment services.

METHODS: A cluster-randomized controlled trial was conducted in Rakhine State to assess the efficacy of ITNs in preventing malaria and anaemia in children and their secondary effects on nutrition and development. The data were aggregated for each village to obtain cluster-level infection rates. **In total 8,175 children under 10 years of age were followed up for 10 months**, which included the main malaria transmission period. The incidence and prevalence of Plasmodium falciparum and Plasmodium vivax infections, and the biting behaviour of Anopheles mosquitoes in the area were studied concurrently. The trial data along with costs for current recommended treatment practices were modelled to estimate the cost-effectiveness of ITNs compared with, or in addition to extending the coverage of early diagnosis and treatment services.

RESULTS: In aggregate, malaria infections, spleen rates, haemoglobin concentrations, and weight for height, did not differ significantly during the study period between villages with and without ITNs, with a weighted mean difference of -2.6 P. falciparum episodes per 1,000 weeks at risk (95% Confidence Interval -7 to 1.8). **In areas with a higher incidence of malaria there was some evidence ITN protective efficacy. The economic analysis indicated that, despite the uncertainty and variability in their protective efficacy in the different study sites, ITN could still be cost-effective, but not if they displaced funding for early diagnosis and effective treatment which is substantially more cost-effective**.

CONCLUSION: In Western Myanmar deployment of ITNs did not provide consistent protection against malaria in children living in malaria endemic villages. Early diagnosis and effective treatment is a more cost effective malaria control strategy than deployment of ITNs in this area where the main vector bites early in the evening, often before people are protected by an ITN.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24119916/

Comment
This is an important study, because it points to the issue that comprehensive approaches are needed to tackle any condition, even for malaria, where ITNs have been the single most important intervention leading to major reductions in malaria incidence in endemic countries worldwide in the past decade, early diagnosis and treatment are essential components of a malaria program. Shows the value of RCTs in identifying benefits and context in which interventions will be effective, or be insufficient to have a major impact on outcomes.

Other preventative interventions

PLoS One. 2013 Aug 14;8(8):e70664. doi: 10.1371/journal.pone.0070664. eCollection 2013.

Can topical insect repellents reduce malaria? A cluster-randomised controlled trial of the insect repellent N,N-diethyl-m-toluamide (DEET) in Lao PDR.

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BACKGROUND:
Mosquito vectors of malaria in Southeast Asia readily feed outdoors making malaria control through indoor insecticides such as long-lasting insecticidal nets (LLINs) and indoor residual spraying more difficult. Topical insect repellents may be able to protect users from outdoor biting, thereby providing additional protection above the current best practice of LLINs.

METHODS AND FINDINGS:
A double blind, household randomised, placebo-controlled trial of insect repellent to reduce malaria was carried out in southern Lao PDR to determine whether the use of repellent and long-lasting insecticidal nets (LLINs) could reduce malaria more than LLINs alone. A total of 1,597 households, including 7,979 participants, were recruited in June 2009 and April 2010. Equal group allocation, stratified by village, was used to randomise **795 households to a 15% DEET lotion and the remainder were given a placebo lotion**. Participants, field staff and data analysts were blinded to the group assignment until data analysis had been completed. All households received new LLINs. **Participants were asked to apply their lotion to exposed skin every evening and sleep under the LLINs each night**. Plasmodium falciparum and P. vivax cases were actively identified by monthly rapid diagnostic tests. **Intention to treat analysis found no effect from the use of repellent on malaria incidence (hazard ratio: 1.00, 95% CI: 0.99-1.01, p=0.868).** A higher socio-economic score was found to significantly decrease malaria risk (hazard ratio: 0.72, 95% CI: 0.58-0.90, p=0.004). Women were also found to have a reduced risk of infection (hazard ratio: 0.59, 95% CI: 0.37-0.92, p=0.020). According to protocol analysis which excluded participants using the lotions less than 90% of the time found similar results with no effect from the use of repellent.

CONCLUSIONS: **This randomised controlled trial suggests that topical repellents are not a suitable intervention in addition to LLINs against malaria amongst agricultural populations in southern Lao PDR.** These results are also likely to be applicable to much of the Greater Mekong Sub-region.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23967083/

Cochrane Database Syst Rev. 2013 Dec 9;12:CD008846. doi: 10.1002/14651858.CD008846.pub2.
Mass drug administration for malaria.
Poirot E[1], Skarbinski J, Sinclair D, Kachur SP, Slutsker L, Hwang J.

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BACKGROUND: Mass drug administration (MDA), defined as the empiric administration of a therapeutic antimalarial regimen to an entire population at the same time, has been a historic component of many malaria control and elimination programmes, but is not currently recommended. With renewed interest in MDA and its role in malaria elimination, this review aims to summarize the findings from existing research studies and program experiences of MDA strategies for reducing malaria burden and transmission.

OBJECTIVES: To assess the impact of antimalarial MDA on population asexual parasitaemia prevalence, parasitaemia incidence, gametocytaemia prevalence, anaemia prevalence, mortality and MDA-associated adverse events.

SEARCH METHODS: We searched the Cochrane Infectious Disease Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE+, EMBASE, to February 2013. We also searched CABS Abstracts, LILACS, reference lists, and recent conference proceedings.

SELECTION CRITERIA:
Cluster-randomized trials and non-randomized controlled studies comparing therapeutic MDA versus placebo or no MDA, and uncontrolled before-and-after studies comparing post-MDA to baseline data were selected. Studies administering intermittent preventive treatment (IPT) to sub-populations (for example, pregnant women, children or infants) were excluded.

DATA COLLECTION AND ANALYSIS: Two authors independently reviewed studies for inclusion, extracted data and assessed risk of bias. Studies were stratified by study design and then subgrouped by endemicity, by co-administration of 8-aminoquinoline plus schizonticide drugs and by plasmodium species. The quality of evidence was assessed using the GRADE approach.

MAIN RESULTS: Two cluster-randomized trials, eight non-randomized controlled studies and 22 uncontrolled before-and-after studies are included in this review. Twenty-two studies (29 comparisons) compared MDA to placebo or no intervention of which two comparisons were conducted in areas of low endemicity (≤5%), 12 in areas of moderate endemicity (6-39%) and 15 in areas of high endemicity (≥ 40%). Ten studies evaluated MDA plus other vector control

measures. The studies used a wide variety of MDA regimens incorporating different drugs, dosages, timings and numbers of MDA rounds. Many of the studies are now more than 30 years old. Areas of low endemicity (≤5%)Within the first month post-MDA, a single uncontrolled before-and-after study conducted in 1955 on a small Taiwanese island reported a much lower prevalence of parasitaemia following a single course of chloroquine compared to baseline (1 study, very low quality evidence). This lower parasite prevalence was still present after more than 12 months (one study, very low quality evidence). In addition, one cluster-randomized trial evaluating MDA in a low endemic setting reported zero episodes of parasitaemia at baseline, and throughout five months of follow-up in both the control and intervention arms (one study, very low quality evidence). Areas of moderate endemicity (6-39%)Within the first month post-MDA, the prevalence of parasitaemia was much lower in three non-randomized controlled studies from Kenya and India in the 1950s (RR 0.03, 95% CI 0.01 to 0.08, three studies, moderate quality evidence), and in three uncontrolled before-and-after studies conducted between 1954 and 1961 (RR 0.29, 95% CI 0.17 to 0.48, three studies,low quality evidence).The longest follow-up in these settings was four to six months. At this time point, the prevalence of parasitaemia remained substantially lower than controls in the two non-randomized controlled studies (RR 0.18, 95% CI 0.10 to 0.33, two studies, low quality evidence). In contrast, the two uncontrolled before-and-after studies found mixed results: one found no difference and one found a substantially higher prevalence compared to baseline (not pooled, two studies, very low quality evidence). Areas of high endemicity (≥40%)Within the first month post-MDA, the single cluster-randomized trial from the Gambia in 1999 found no significant difference in parasite prevalence (one study, low quality evidence). However, prevalence was much lower during the MDA programmes in three non-randomized controlled studies conducted in the 1960s and 1970s (RR 0.17, 95% CI 0.11 to 0.27, three studies, moderate quality evidence), and within one month of MDA in four uncontrolled before-and-after studies (RR 0.37, 95% CI 0.28 to 0.49, four studies,low quality evidence).Four trials reported changes in prevalence beyond three months. In the Gambia, the single cluster-randomized trial found no difference at five months (one trial, moderate quality evidence). The three uncontrolled before-and-after studies had mixed findings with large studies from Palestine and Cambodia showing sustained reductions at four months and 12 months, respectively, and a small study from Malaysia showing no difference after four to six months of follow-up (three studies,low quality evidence). 8-aminoquinolines We found no studies directly comparing MDA regimens that included 8-aminoquinolines with regimens that did not. In a crude subgroup analysis with a limited number of studies, we were unable to detect any evidence of additional benefit of primaquine in moderate- and high-transmission settings. Plasmodium species In studies that reported species-specific outcomes, the same interventions resulted in a larger impact on Plasmodium falciparum compared to P. vivax.

AUTHORS' CONCLUSIONS:
MDA appears to reduce substantially the initial risk of malaria parasitaemia. However, few studies showed sustained impact beyond six months post-MDA, and those that did were conducted on small islands or in highland settings. To assess whether there is an impact of MDA on malaria transmission in the longer term requires more quasi experimental studies with the intention of elimination, especially in low- and moderate-transmission settings. These studies need to address any long-term outcomes, any potential barriers for community uptake, and contribution to the development of drug resistance.

http://onlinelibrary.wiley.com/store/10.1002/14651858.CD008846.pub2/asset/CD008846.pdf?v=1&t=hxd2wha6&s=e37e4f6479591281d786853cfde7ff52e2901187

Treatment of uncomplicated malaria

Lancet Infect Dis. 2014 Feb;14(2):130-9. doi: 10.1016/S1473-3099(13)70268-8. Epub 2013 Nov 13.

Single dose primaquine for clearance of Plasmodium falciparum gametocytes in children with uncomplicated malaria in Uganda: a randomised, controlled, double-blind, dose-ranging trial.

Eziefula AC, Bousema T, Yeung S, Kamya M, Owaraganise A, Gabagaya G, Bradley J, Grignard L, Lanke KH, Wanzira H, Mpimbaza A, Nsobya S, White NJ, Webb EL, Staedke SG[3], Drakeley C.

BACKGROUND: **Primaquine is the only available drug that clears mature Plasmodium falciparum gametocytes in infected human hosts, thereby preventing transmission of malaria to mosquitoes.** However, concerns about dose-dependent haemolysis in people with glucose-6-phosphate dehydrogenase (G6PD) deficiencies have limited its use. We assessed the dose-response association of single-dose primaquine for gametocyte clearance and for safety in P falciparum malaria.

METHODS: We undertook this randomised, double-blind, placebo-controlled trial with four parallel groups in Jinja district, eastern Uganda. **We randomly allocated Ugandan children aged 1-10 years with uncomplicated falciparum malaria and normal G6PD enzyme function to receive artemether-lumefantrine, combined with either placebo or with 0.1 mg/kg, 0.4 mg/kg, or 0.75 mg/kg (WHO reference dose) primaquine base**. Randomisation was done with computer-generated four-digit treatment assignment codes allocated to random dose groups in block sizes of 16. Study staff who provided care or assessed outcomes and the participants remained masked to the intervention group after assignment. **The primary efficacy endpoint was the non-inferiority of the mean duration of gametocyte carriage in the test doses compared with the reference group of 0.75 mg primaquine per kg, with a non-inferiority margin of 2.5 days.** The primary safety endpoint was the superiority of the arithmetic mean maximum decrease in haemoglobin concentration from enrolment to day 28 of follow-up in the primaquine treatment groups compared with placebo, with use of significance testing of pairwise comparisons with a cutoff of p=0.05. The trial is registered with ClinicalTrials.gov, number NCT01365598.

FINDINGS: **We randomly allocated 468 participants to receive artemether-lumefantrine combined with placebo (119 children) or with 0.1 mg/kg (116), 0.4 mg/kg (116), or 0.75 mg/kg (117) primaquine base. The mean duration of gametocyte carriage was 6.6 days (95% CI 5.3-7.8) in the 0.75 mg/kg reference group, 6.3 days (5.1-7.5) in the 0.4 mg/kg primaquine group (p=0.74), 8.0 days (6.6-9.4) in the 0.1 mg/kg primaquine group (p=0.14), and 12.4 days (9.9-15.0) in the placebo group (p<0.0001).** No children showed evidence of treatment-related haemolysis, and the mean maximum decrease in haemoglobin concentration was not associated with the dose of primaquine received-it did not differ significantly compared with placebo (10.7 g/L, SD 11.1) in the 0.1 mg/kg (11.4 g/L, 9.4; p=0.61), 0.4 mg/kg (11.3 g/L, 10.0; p=0.67), or 0.75 mg/kg (12.7 g/L, 8.2; p=0.11) primaquine groups.

INTERPRETATION: **We conclude that 0.4 mg/kg primaquine has similar gametocytocidal efficacy to the reference 0.75 mg/kg primaquine dose, but a dose of 0.1 mg/kg was inconclusive for non-inferiority.** Our findings call for the prioritisation of further trials into the

efficacy and safety of doses of primaquine between 0.1 mg/kg and 0.4 mg/kg (including the dose of 0.25 mg/kg recently recommended by WHO), in view of the potential for widespread use of the drug to block malaria transmission.

Single low-dose primaquine to reduce malaria transmission. [Lancet Infect Dis. 2014]

http://linkinghub.elsevier.com/retrieve/pii/S1473-3099(13)70268-8

Malar J. 2013 Jul 19;12:254. doi: 10.1186/1475-2875-12-254.

A randomized trial of artemether-lumefantrine and dihydroartemisinin-piperaquine in the treatment of uncomplicated malaria among children in western Kenya.

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BACKGROUND:
Artemether-lumefantrine (AL) was adopted as first-line treatment for uncomplicated malaria in Kenya in 2006. Monitoring drug efficacy at regular intervals is essential to prevent unnecessary morbidity and mortality. The efficacy of AL and dihydroartemisinin-piperaquine (DP) were evaluated for the treatment of uncomplicated malaria in children aged six to 59 months in western Kenya.

METHODS: From October 2010 to August 2011, children with fever or history of fever with uncomplicated Plasmodium falciparum mono-infection were enrolled in an in vivo efficacy trial in accordance with World Health Organization (WHO) guidelines. The **children were randomized to treatment with a three-day course of AL or DP and efficacy outcomes were measured at 28 and 42 days after treatment initiation**.

RESULTS: A total of 137 children were enrolled in each treatment arm. **There were no early treatment failures and all children except one had cleared parasites by day 3.** Polymerase chain reaction (PCR)-uncorrected adequate clinical and parasitological response rate (ACPR) was 61% in the AL arm and 83% in the DP arm at day 28 ($p = 0.001$). PCR-corrected ACPR at day 28 was 97% in the AL group and 99% in the DP group, and it was 96% in both arms at day 42.

CONCLUSIONS: **AL and DP remain efficacious for the treatment of uncomplicated malaria among children in western Kenya.** The longer half-life of piperaquine relative to lumefantrine may provide a prophylactic effect, accounting for the lower rate of re-infection in the first 28 days after treatment in the DP arm.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23870627/

J Infect Dis. 2013 Dec 1;208(11):1906-13. doi: 10.1093/infdis/jit407. Epub 2013 Aug 6.

A randomized comparison of dihydroartemisinin-piperaquine and artesunate-amodiaquine combined with primaquine for radical treatment of vivax malaria in Sumatera, Indonesia.

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BACKGROUND: A high prevalence of chloroquine-resistant Plasmodium vivax in Indonesia has shifted first-line treatment to artemisinin-based combination therapies, combined with primaquine (PQ) for radical cure. Which combination is most effective and safe remains to be established.

METHODS: **We conducted a prospective open-label randomized comparison of 14 days of PQ (0.25 mg base/kg) plus either artesunate-amodiaquine (AAQ + PQ) or dihydroartemisinin-piperaquine (DHP + PQ) for the treatment of uncomplicated monoinfection P. vivax malaria in North Sumatera, Indonesia**. Patients were randomized and treatments were given without prior testing for G6PD status. The primary outcome was parasitological failure at day 42. Patients were followed up to 1 year.

RESULTS: Between December 2010 and April 2012, 331 patients were included. After treatment with AAQ + PQ, recurrent infection occurred in 0 of 167 patients within 42 days and in 15 of 130 (11.5%; 95% confidence interval [CI], 6.6%-18.3%) within a year. With DHP + PQ, this was 1 of 164 (0.6%; 95% CI, 0.01%-3.4%) and 13 of 143 (9.1%; 95% CI, 4.9%-15.0%), respectively (P > .2). **Intravascular hemolysis occurred in 5 patients, of which 3 males were hemizygous for the G6PD-Mahidol mutation**. Minor adverse events were more frequent with AAQ + PQ.

CONCLUSIONS: In North Sumatera, Indonesia, AAQ and DHP, both combined with PQ, were effective for blood-stage parasite clearance of uncomplicated P. vivax malaria. Both treatments were safe, but DHP + PQ was better tolerated.
CLINICAL TRIALS REGISTRATION: NCT01288820.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23926329/

Malar J. 2013 Jul 17;12:251. doi: 10.1186/1475-2875-12-251.

Efficacy of artesunate-amodiaquine and artemether-lumefantrine fixed-dose combinations for the treatment of uncomplicated Plasmodium falciparum malaria among children aged six to 59 months in Nimba County, Liberia: an open-label randomized non-inferiority trial.

Schramm B[1], Valeh P, Baudin E, Mazinda CS, Smith R, Pinoges L, Dhorda M, Boum Y 2nd, Sundaygar T, Zolia YM, Jones JJ, Comte E, Houzé P, Jullien V, Carn G, Kiechel JR, Ashley EA, Guérin PJ.

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BACKGROUND: Prospective efficacy monitoring of anti-malarial treatments is imperative for timely detection of resistance development. The in vivo efficacy of artesunate-amodiaquine (ASAQ) fixed-dose combination (FDC) was compared to that of artemether-lumefantrine (AL) among children aged six to 59 months in Nimba County, Liberia, where Plasmodium falciparum malaria is endemic and efficacy data are scarce.

METHODS: An open-label, randomized controlled non-inferiority trial compared the genotyping adjusted day 42 cure rates of ASAQ FDC (ASAQ Winthrop®) to AL (Coartem®) in 300 children aged six to 59 months with uncomplicated falciparum malaria. Inclusion was between December 2008 and May 2009. Randomization (1:1) was to a three-day observed oral regimen (ASAQ: once a day; AL: twice a day, given with fatty food). Day 7 desethylamodiaquine and lumefantrine blood-concentrations were also measured.

RESULTS: The day 42 genotyping-adjusted cure rate estimates were 97.3% [95% CI: 91.6-99.1] for ASAQ and 94.2% [88.1-97.2] for AL (Kaplan-Meier survival estimates). The difference in day 42 cure rates was -3.1% [upper limit 95% CI: 1.2%]. These results were confirmed by observed proportion of patients cured at day 42 on the per-protocol population. Parasite clearance was 100% (ASAQ) and 99.3% (AL) on day 3. The probability to remain free of re-infection was 0.55 [95% CI: 0.46-0.63] (ASAQ) and 0.66 [0.57-0.73] (AL) (p = 0.017).

CONCLUSIONS: **Both ASAQ and AL were highly efficacious and ASAQ was non-inferior to AL.** The proportion of patients with re-infection was high in both arms in this highly endemic setting. In 2010, ASAQ FDC was adopted as the first-line national treatment in Liberia. Continuous efficacy monitoring is recommended.
TRIAL REGISTRATION:
The protocols were registered with Current Controlled Trials, under the identifier numbers ISRCTN51688713, ISRCTN40020296.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23866774/

Trop Med Int Health. 2014 Apr;19(4):469-75. doi: 10.1111/tmi.12274. Epub 2014 Feb 5.

Effectiveness of artesunate-amodiaquine vs. artemether-lumefantrine for the treatment of uncomplicated falciparum malaria in Nanoro, Burkina Faso: a non-inferiority randomised trial.

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OBJECTIVES: Artemisinin-based combination therapies (ACTs) are essential for the effective control of falciparum malaria in endemic countries. However, in most countries, such choice has been carried out without knowing their effectiveness when deployed in real-life conditions, that is, when treatment is not directly observed. We report here the results of a study assessing the effectiveness of the two ACTs currently recommended in Burkina Faso for the

treatment of uncomplicated malaria, that is, **artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ)**.

METHODS: Between September 2008 and January 2010, **340 children were randomised to one of the two study arms and followed up for 42 days.** Treatment was administered according to routine practices, that is, the first dose was given by study nurses who explained to the parent/guardian how to administer the other doses at home during the following 2 days.

RESULTS: **The results showed a significantly higher unadjusted adequate clinical and parasitological response in the ASAQ (58.4%) than in the AL arm (46.1%) at day 28 but these trends were similar after correction with PCR data (ASAQ (89.7%) and AL (89.8%)).** New infections started to appear after day 14, first in the AL and then in the ASAQ arm but at day 42 day of follow-up we observed no difference in the occurrence of recrudescent infection.

CONCLUSION: Despite a lower cure rate than those reported in efficacy studies in which the treatment administration was directly observed, **both AL and ASAQ can still be used for the treatment of uncomplicated malaria in Burkina Faso.**

Cochrane Database Syst Rev. 2014 Mar 4;3:CD006404. doi: 10.1002/14651858.CD006404.pub2.

Artesunate plus pyronaridine for treating uncomplicated Plasmodium falciparum malaria.

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BACKGROUND: The World Health Organization (WHO) recommends that people with uncomplicated Plasmodium falciparum malaria are treated using Artemisinin-based Combination Therapy (ACT). **ACT combines three-days of a short-acting artemisinin derivative with a longer-acting antimalarial which has a different mode of action.** Pyronaridine has been reported as an effective antimalarial over two decades of use in parts of Asia, and is currently being evaluated as a partner drug for artesunate.

OBJECTIVES: To evaluate the efficacy and safety of artesunate-pyronaridine compared to alternative ACTs for treating people with uncomplicated P. falciparum malaria.

SEARCH METHODS: We searched the Cochrane Infectious Diseases Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL), published in The Cochrane Library; MEDLINE; EMBASE; LILACS; ClinicalTrials.gov; the metaRegister of Controlled Trials (mRCT); and the WHO International Clinical Trials Search Portal up to 16 January 2014. We searched reference lists and conference abstracts, and contacted experts for information about ongoing and unpublished trials.

SELECTION CRITERIA: Randomized controlled trials of artesunate-pyronaridine versus other ACTs in adults and children with uncomplicated P. falciparum malaria.For the safety

analysis, we also included adverse events data from trials comparing any treatment regimen containing pyronaridine with regimens not containing pyronaridine.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed trial eligibility and risk of bias, and extracted data. We combined dichotomous data using risk ratios (RR) and continuous data using mean differences (MD), and presented all results with a 95% confidence interval (CI). We used the GRADE approach to assess the quality of evidence.

MAIN RESULTS: We included six randomized controlled trials enrolling 3718 children and adults. Artesunate-pyronaridine versus artemether-lumefantrine. **In two multicentre trials, enrolling mainly older children and adults from west and south-central Africa, both artesunate-pyronaridine and artemether-lumefantrine had fewer than 5% PCR adjusted treatment failures during 42 days of follow-up, with no differences between groups (two trials, 1472 participants, low quality evidence).** There were fewer new infections during the first 28 days in those given artesunate-pyronaridine (PCR-unadjusted treatment failure: RR 0.60, 95% CI 0.40 to 0.90, two trials, 1720 participants, moderate quality evidence), but no difference was detected over the whole 42 day follow-up (two trials, 1691 participants, moderate quality evidence). Artesunate-pyronaridine versus artesunate plus mefloquineIn one multicentre trial, enrolling mainly older children and adults from South East Asia, both artesunate-pyronaridine and artesunate plus mefloquine had fewer than 5% PCR adjusted treatment failures during 28 days follow-up (one trial, 1187 participants, moderate quality evidence). PCR-adjusted treatment failures were 6% by day 42 for these treated with artesunate-pyronaridine, and 4% for those with artesunate-mefloquine (RR 1.64, 95% CI 0.89 to 3.00, one trial, 1116 participants, low quality evidence). Again, there were fewer new infections during the first 28 days in those given artesunate-pyronaridine (PCR-unadjusted treatment failure: RR 0.35, 95% CI 0.17 to 0.73, one trial, 1720 participants, moderate quality evidence), but no differences were detected over the whole 42 days (one trial, 1146 participants, low quality evidence). Adverse effectsSerious adverse events were uncommon in these trials, with no difference detected between artesunate-pyronaridine and comparator ACTs. The analysis of liver function tests showed biochemical elevation were four times more frequent with artesunate-pyronaridine than with the other antimalarials (RR 4.17, 95% CI 1.38 to 12.62, four trials, 3523 participants, moderate quality evidence).

AUTHORS' CONCLUSIONS: **Artesunate-pyronaridine performed well in these trials compared to artemether-lumefantrine and artesunate plus mefloquine, with PCR-adjusted treatment failure at day 28 below the 5% standard set by the WHO.** Further efficacy and safety studies in African and Asian children are required to clarify whether this combination is an option for first-line treatment.

Malar Res Treat. 2014;2014:625905. doi: 10.1155/2014/625905. Epub 2014 Jan 19.

Effect of iron/folic Acid supplementation on the outcome of malaria episodes treated with sulfadoxine-pyrimethamine.

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Folic acid supplementation may potentially alter the efficacy of sulfadoxine-pyrimethamine (SP) treatment in children with malaria. However, there is lack of evidence from randomized controlled trials and effects of folic acid supplementation on clinical efficacy of SP therapy remain moderately understood among children. **In a double masked, placebo-controlled trial among preschool children in Pemba Island (Tanzania), iron and folic acid supplementation (Fe/FA) showed an increased risk of hospitalizations and death.** In the present paper, we evaluated if folic acid supplementation reduced the efficacy of malaria treatment and thereby contributed to observed adverse effects. During the study, 1648 children had confirmed malarial episodes and received either sulphadoxine-pyrimethamine (SP) treatment and iron folic acid or SP treatment and placebo. These children were evaluated for recovery and incidence of hospitalization during the next 15, 30, and 140 days. Two groups did not differ in malarial episode or hospitalization rate on subsequent 15, 30, and 140 days. Altered efficacy of SP by folic acid was not observed and did not contribute to adverse events in the previous trial. This trial is registered with Controlled-trials.com ISRCTN59549825.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24575311/

Comment
An important follow-up trial to investigate the results of a influential study which helped change WHO's recommendations on routine iron / folic acid supplementation in malaria-endemic areas. This study showed that the observed effect of increased hospitalisations and deaths in the iron-folic acid supplemented group was not due to folic acid reducing the effect of sulfadoxine-pyrimethamine. Other trials this year have not shown a detrimental effect of iron supplementation on morbidity, and WHIO's recommendations are now:

- *In settings where the prevalence of anaemia in preschool (24–59 months) or school-age (5–12 years) children is 20% or higher, WHO recommends the intermittent use of iron supplements as a public health intervention to improve iron status and reduce the risk of anaemia among children.*
- *In malaria-endemic areas, the provision of iron supplements should be implemented in conjunction with measures to prevent, diagnose and treat malaria.*

http://www.who.int/elena/titles/iron_infants_malaria/en/

Malar J. 2014 Jan 28;13:32. doi: 10.1186/1475-2875-13-32.

Early parasite clearance following artemisinin-based combination therapy among Ugandan children with uncomplicated Plasmodium falciparum malaria.

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BACKGROUND: Artemisinin-based combination therapy (ACT) is widely recommended as first-line therapy for uncomplicated Plasmodium falciparum malaria worldwide. **Artemisinin resistance has now been reported in Southeast Asia with a clinical phenotype manifested by slow parasite clearance.** Although there are no reliable reports of artemisinin resistance in Africa, there is a need to better understand the dynamics of parasite clearance in African children treated with ACT in order to better detect the emergence of artemisinin resistance.

METHODS: **Data from a cohort of Ugandan children four to five years old, enrolled in a longitudinal, randomized, clinical trial comparing two leading ACT, artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP), were analysed**. For all episodes of uncomplicated P. falciparum malaria over a 14-month period, daily blood smears were performed for three days following the initiation of therapy. Associations between pre-treatment variables of interest and persistent parasitaemia were estimated using multivariate, generalized, estimating equations with adjustment for repeated measures in the same patient.

RESULTS: **A total of 202 children were included, resulting in 416 episodes of malaria treated with AL and 354 episodes treated with DP**. The prevalence of parasitaemia on days 1, 2, and 3 following initiation of therapy was 67.6, 5.6 and 0% in those treated with AL, and 52.2, 5.7 and 0.3% in those treated with DP. **Independent risk factors for persistent parasitaemia on day 1 included treatment with AL vs DP (RR = 1.34, 95% CI 1.20-1.50, p < 0.001), having a temperature ≥38.0°C vs < 37.0°C (RR = 1.19, 95% CI 1.05-1.35, p = 0.007) and having a parasite density >20,000/μL vs <4,000/μL (RR = 3.37, 95% CI 2.44-4.49, p < 0.001).** Independent risk factors for having persistent parasitaemia on day 2 included elevated temperature, higher parasite density, and being HIV infected.

CONCLUSIONS: Among Ugandan children, parasite clearance following treatment with AL or DP was excellent with only one of 752 patients tested having a positive blood slide three days after initiation of therapy. **The type of ACT given, pre-treatment temperature, pre-treatment parasite density and HIV status were associated with differences in persistent parasitaemia, one or two days following therapy.**

TRIAL REGISTRATION:
Current Controlled Trials Identifier NCT00527800.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24468007/

Cochrane Database Syst Rev. 2014 Jan 20;1:CD010927. doi: 10.1002/14651858.CD010927.

Dihydroartemisinin-piperaquine for treating uncomplicated Plasmodium falciparum malaria.

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BACKGROUND: The World Health Organization (WHO) recommends Artemisinin-based Combination Therapy (ACT) for treating uncomplicated Plasmodium falciparum malaria. This review aims to assist the decision-making of malaria control programmes by providing an

overview of the relative effects of dihydroartemisinin-piperaquine (DHA-P) versus other recommended ACTs.

OBJECTIVES: To evaluate the effectiveness and safety of DHA-P compared to other ACTs for treating uncomplicated P. falciparum malaria in adults and children.

SEARCH METHODS: We searched the Cochrane Infectious Diseases Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL) published in The Cochrane Library; MEDLINE; EMBASE; LILACS, and the metaRegister of Controlled Trials (mRCT) up to July 2013.

SELECTION CRITERIA: Randomized controlled trials comparing a three-day course of DHA-P to a three-day course of an alternative WHO recommended ACT in uncomplicated P. falciparum malaria.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed trials for eligibility and risk of bias, and extracted data. We analysed primary outcomes in line with the WHO 'Protocol for assessing and monitoring antimalarial drug efficacy' and compared drugs using risk ratios (RR) and 95% confidence intervals (CI). Secondary outcomes were effects on gametocytes, haemoglobin, and adverse events. We assessed the quality of evidence using the GRADE approach.

MAIN RESULTS: We included 27 trials, enrolling 16,382 adults and children, and conducted between 2002 and 2010. Most trials excluded infants aged less than six months and pregnant women. **DHA-P versus artemether-lumefantrineIn Africa, over 28 days follow-up, DHA-P is superior to artemether-lumefantrine at preventing further parasitaemia (PCR-unadjusted treatment failure: RR 0.34, 95% CI 0.30 to 0.39, nine trials, 6200 participants, high quality evidence), and although PCR-adjusted treatment failure was below 5% for both ACTs, it was consistently lower with DHA-P (PCR-adjusted treatment failure: RR 0.42, 95% CI 0.29 to 0.62, nine trials, 5417 participants, high quality evidence).** DHA-P has a longer prophylactic effect on new infections which may last for up to 63 days (PCR-unadjusted treatment failure: RR 0.71, 95% CI 0.65 to 0.78, two trials, 3200 participants, high quality evidence).**In Asia and Oceania, no differences have been shown at day 28 (four trials, 1143 participants, moderate quality evidence), or day 63 (one trial, 323 participants, low quality evidence).**Compared to artemether-lumefantrine, no difference was seen in prolonged QTc (low quality evidence), and no cardiac arrhythmias were reported. The frequency of other adverse events is probably similar with both combinations (moderate quality evidence). DHA-P versus artesunate plus mefloquineIn Asia, over 28 days follow-up, DHA-P is as effective as artesunate plus mefloquine at preventing further parasitaemia (PCR-unadjusted treatment failure: eight trials, 3487 participants, high quality evidence). Once adjusted by PCR to exclude new infections, treatment failure at day 28 was below 5% for both ACTs in all eight trials, but lower with DHA-P in two trials (PCR-adjusted treatment failure: RR 0.41 95% CI 0.21 to 0.80, eight trials, 3482 participants, high quality evidence). Both combinations contain partner drugs with very long half-lives and no consistent benefit in preventing new infections has been seen over 63 days follow-up (PCR-unadjusted treatment failure: five trials, 2715 participants, moderate quality evidence).In the only trial from South America, there were fewer recurrent parastaemias over 63 days with artesunate plus mefloquine (PCR-unadjusted treatment failure: RR 6.19, 95% CI 1.40 to 27.35, one trial, 445 participants, low quality evidence), but no differences were seen once adjusted for new infections (PCR-adjusted treatment failure: one trial, 435 participants, low quality evidence).DHA-P is associated with less nausea, vomiting, dizziness, sleeplessness, and palpitations compared to artesunate plus mefloquine (moderate

quality evidence). DHA-P was associated with more frequent prolongation of the QTc interval (low quality evidence), but no cardiac arrhythmias were reported.

AUTHORS' CONCLUSIONS: **In Africa, dihydroartemisinin-piperaquine reduces overall treatment failure compared to artemether-lumefantrine, although both drugs have PCR-adjusted failure rates of less than 5%.** In Asia, dihydroartemisinin-piperaquine is as effective as artesunate plus mefloquine, and is better tolerated.

http://onlinelibrary.wiley.com/store/10.1002/14651858.CD010927/asset/CD010927.pdf?v=1&t=hxd2zooz&s=c8c2d62d008c65aa31aafc9a5f631458319a2d1a

J Infect Dis. 2013 Dec 15;208(12):2017-24. doi: 10.1093/infdis/jit431. Epub 2013 Aug 14.

Residual Plasmodium falciparum parasitemia in Kenyan children after artemisinin-combination therapy is associated with increased transmission to mosquitoes and parasite recurrence.

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BACKGROUND: **Parasite clearance time after artemisinin-based combination therapy (ACT) may be increasing in Asian and African settings**. The association between parasite clearance following ACT and transmissibility is currently unknown.

METHODS: We determined parasite clearance dynamics by duplex quantitative polymerase chain reaction (qPCR) in samples collected in the first 3 days after treatment of uncomplicated malaria with ACT. Gametocyte carriage was determined by Pfs25 quantitative nucleic acid sequence-based amplification assays; infectiousness to mosquitoes by membrane-feeding assays on day 7 after treatment.

RESULTS: **Residual parasitemia was detected by qPCR in 31.8% (95% confidence interval [CI], 24.6-39.8) of the children on day 3 after initiation of treatment**. Residual parasitemia was associated with a 2-fold longer duration of gametocyte carriage (P = .0007), a higher likelihood of infecting mosquitoes (relative risk, 1.95; 95% CI, 1.17-3.24; P = .015), and a higher parasite burden in mosquitoes (incidence rate ratio, 2.92; 95% CI, 1.61-5.31; P < .001). Children with residual parasitemia were also significantly more likely to experience microscopically detectable parasitemia during follow-up (relative risk, 11.25; 95% CI, 4.08-31.01; P < .001).

CONCLUSIONS: **Residual submicroscopic parasitemia is common after ACT and is associated with a higher transmission potential. Residual parasitemia may also have consequences for individual patients because of its higher risk of recurrent parasitemia.**

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23945376/

J Clin Virol. 2013 Sep;58(1):276-8. doi: 10.1016/j.jcv.2013.06.008. Epub 2013 Jul 1.

An artesunate-containing antimalarial treatment regimen did not suppress cytomegalovirus viremia.

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BACKGROUND: Additional drugs are needed for the treatment of cytomegalovirus (CMV) infection. Artesunate is an antimalarial drug that has activity against CMV in vitro and in a rodent model. Only a small number of case reports are available describing the clinical effects of artesunate on CMV infection, and these yielded inconsistent results.

OBJECTIVE: To evaluate the effect of artesunate on CMV infection, using blood samples collected from children who participated in malaria treatment trials.

STUDY DESIGN: **Quantitative CMV DNA PCR was performed on dried blood spots collected from 494 Ugandan children, who were randomized either to artesunate plus amodiaquine or sulfadoxine-pyrimethamine plus amodiaquine for acute malaria infection**. Poisson regression was used to compare treatment regimens with respect to the change in the frequency and quantity of CMV detected that occurred before and after treatment.

RESULTS: **CMV was detected in 11.4% of children immediately prior to treatment and 10.7% 3 days later (p=0.70).** The average quantity of CMV was 0.30 log10 copies per million cells higher on day 3 than at treatment initiation (95% CI 0.01-0.58, p=0.041). There was no measurable difference in either the frequency or quantity of CMV detected in blood between children randomized to the two treatment arms.

CONCLUSIONS: **A standard 3-day artesunate-containing antimalarial regimen had no detectable effect on CMV viremia in children with malaria.** Longer treatment courses and/or higher doses of artesunate than those routinely used for malaria may be required for effective treatment of CMV infection.

Treatment of severe or complicated malaria

*** Cochrane Database Syst Rev. 2014 May 29;5:CD009964. doi: 10.1002/14651858.CD009964.pub2.

Pre-referral rectal artesunate for severe malaria.

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BACKGROUND: Severe or complicated malaria is a medical emergency and people die as a result of delays in starting treatment. Most patients need parenteral treatment, and in primary healthcare facilities, where intravenous therapy is not available but intramuscular injections can be given, intramuscular quinine, artesunate, and artemether have been used before transporting patients to hospital.However, in rural settings with limited access to health care, intramuscular injections may also be unavailable. In these situations, rectal artesunate given prior to transfer to hospital by volunteers with little medical training, may be a feasible option.

OBJECTIVES: **To evaluate the effects of pre-referral treatment with rectal artesunate on mortality and morbidity in people with severe malaria**.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) published in The Cochrane Library; MEDLINE; EMBASE and LILACS up to 21 May 2014. We also searched the WHO clinical trial registry platform and the metaRegister of Controlled Trials (mRCT) for ongoing trials.

SELECTION CRITERIA: Individual or cluster-randomized controlled trials comparing pre-referral rectal artesunate with placebo or injectable antimalarials in children and children with severe malaria.

DATA COLLECTION AND ANALYSIS: Two authors independently screened titles and abstracts for potentially eligible trials, and extracted data from the included trials. Dichotomous outcomes were summarized using risk ratios (RR) and presented with 95% confidence intervals (95% CI). Where data allowed, we conducted subgroup analyses by age, trial region and whether participants were included in the trial analysis. We assessed the quality of evidence for the most important outcomes using the GRADE approach.

MAIN RESULTS: **One trial met the inclusion criteria; a placebo-controlled trial of 17,826 children and adults living in rural villages in Ghana and Tanzania (Africa) and Bangladesh (Asia).** Villagers with no previous medical training were trained to recognize the symptoms of severe malaria, administer rectal artesunate and refer patients to hospital. The trained villagers were supervised during the trial period. In the African sites only children aged 6 to 72 months were enrolled, whereas in Bangladesh, older children and adults were also enrolled.**In young children (aged 6 to 72 months) there were fewer deaths following rectal artesunate than with placebo (RR 0.74; 95% CI 0.59 to 0.93; one trial; 8050 participants; moderate quality evidence), while in older children and adults there were more deaths in those given rectal artesunate (RR 2.21; 95% CI 1.18 to 4.15; one trial; 4018 participants; low quality evidence)**.In Africa, only 56% of participants reached a secondary healthcare facility within six hours compared to over 90% in Asia. There were no differences between the intervention and control groups in the proportion of participants reaching a healthcare facility within six hours (RR 0.99; 95% CI 0.98 to 1.01; 12,068 participants), or in the proportion with parasitaemia (RR 1.00; 95% CI 0.98 to 1.02; 17,826 participants), or with coma or convulsions on arrival (RR 1.01; 95% CI 0.90 to 1.14; 12,068 participants).There are no existing trials that compare rectal versus intramuscular artesunate.

AUTHORS' CONCLUSIONS: **In rural areas without access to injectable antimalarials rectal artesunate provided before transfer to a referral facility probably reduces mortality in severely ill young children compared to referral without treatment**. However, the unexpected finding of possible higher mortality in older children and adults has to be taken into account in forming any national or local policies about pre-referral rectal artesunate.

Br J Haematol. 2014 Feb;164(3):438-50. doi: 10.1111/bjh.12636.

Blood oxidative stress markers and Plasmodium falciparum malaria in non-immune African children.

Aguilar R[1], Marrocco T, Skorokhod OA, Barbosa A, Nhabomba A, Manaca MN, Guinovart C, Quintó L, Arese P, Alonso PL, Dobaño C, Schwarzer E.

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Converging in vitro evidence and clinical data indicate that oxidative stress may play important roles in Plasmodium falciparum malaria, notably in the pathogenesis of severe anaemia. However, oxidative modifications of the red blood cell (RBC)-membrane by 4-hydroxynonenal (4-HNE) and haemoglobin-binding, previously hypothesized to contribute mechanistically to the pathogenesis of clinical malaria, have not yet been tested for clinical significance. In 349 non-immune Mozambican newborns recruited in a double-blind placebo-controlled chemoprophylaxis trial, oxidative markers including 4-HNE-conjugates and membrane-bound haemoglobin were longitudinally assessed from 2·5 to 24 months of age, at first acute malaria episode and in convalescence. During acute malaria, 4-HNE-conjugates were shown to increase significantly in parasitized and non-parasitized RBCs. In parallel, advanced oxidation protein products (AOPP) rose in plasma. 4-HNE-conjugates correlated with AOPP and established plasma but not with RBC oxidative markers. High individual levels of 4-HNE-conjugates were predictive for increased malaria incidence rates in children until 2 years of life and elevated 4-HNE-conjugates in convalescence accompanied sustained anaemia after a malaria episode, indicating 4-HNE-conjugates as a novel patho-mechanistic factor in malaria. A second oxidative marker, haemoglobin binding to RBC-membranes, hypothesized to induce clearing of RBCs from circulation, was predictive for lower malaria incidence rates. Further studies will show whether or not higher membrane-haemoglobin values at the first malaria episode may provide protection against malaria.

Treatment of vivax malaria

Cochrane Database Syst Rev. 2013 Oct 25;10:CD008492. doi: 10.1002/14651858.CD008492.pub3.

Artemisinin-based combination therapy for treating uncomplicated Plasmodium vivax malaria.

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BACKGROUND: Plasmodium vivax is an important cause of malaria in many parts of Asia and South America, and parasite resistance to the standard treatment (chloroquine) is now high in some parts of Oceania. This review aims to assess the current treatment options in the light of increasing chloroquine resistance.

OBJECTIVES: To compare artemisinin-based combination therapies (ACTs) with alternative antimalarial regimens for treating acute uncomplicated P. vivax malaria.

SEARCH METHODS: We searched the Cochrane Infectious Disease Group Specialized Register; the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; EMBASE; LILACS; and the metaRegister of Controlled Trials (mRCT) up to 28 March 2013 using "vivax" and "arte* OR dihydroarte*" as search terms.

SELECTION CRITERIA: Randomized controlled trials comparing ACTs versus standard therapy, or comparing alternative ACTs, in adults and children with uncomplicated P. vivax malaria.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed trials for eligibility and risk of bias, and extracted data. **We used recurrent parasitaemia prior to day 28 as a proxy for effective treatment of the blood stage parasite, and compared drug treatments using risk ratios (RR) and 95% confidence intervals (CIs).** We used trials following patients for longer than 28 days to assess the duration of the post-treatment prophylactic effect of ACTs. We assessed the quality of the evidence using the GRADE approach.

MAIN RESULTS: We included **14 trials, that enrolled 2592 participants, and were all conducted in Asia and Oceania between 2002 and 2011. ACTs versus chloroquine: ACTs clear parasites from the peripheral blood quicker than chloroquine monotherapy (parasitaemia after 24 hours of treatment: RR 0.42, 95% CI 0.36 to 0.50, four trials, 1652 participants, high quality evidence).**In settings where chloroquine remains effective, ACTs are as effective as chloroquine at preventing recurrent parasitaemias before day 28 (RR 0.58, 95% CI 0.18 to 1.90, five trials, 1622 participants, high quality evidence). In four of these trials, recurrent parasitaemias before day 28 were very low following treatment with both chloroquine and ACTs. The fifth trial, from Thailand in 2011, found increased recurrent parasitaemias following treatment with chloroquine (9%), while they remained low following ACT (2%) (RR 0.25, 95% CI 0.09 to 0.66, one trial, 437 participants).ACT combinations with long half-lives probably also provide a longer prophylactic effect after treatment, with significantly fewer recurrent parasitaemias between day 28 and day 42 or day 63 (RR 0.57, 95% CI 0.40 to 0.82, three trials, 1066 participants, moderate quality evidence). **One trial, from Cambodia, Thailand, India and Indonesia, gave additional primaquine to both treatment groups to reduce the risk of spontaneous relapses. Recurrent parasitaemias after day 28 were lower than seen in the trials that did not give primaquine, but the ACT still appeared to have an advantage (RR 0.27, 95% CI 0.08 to 0.94, one trial, 376 participants, low quality evidence).** ACTs versus alternative ACTs: **In high transmission settings, dihydroartemisinin-piperaquine is probably superior to artemether-lumefantrine, artesunate plus sulphadoxine-pyrimethamine and artesunate plus amodiaquine at preventing recurrent parasitaemias before day 28 (RR 0.20, 95% CI 0.08 to 0.49, three trials, 334 participants, moderate quality evidence).Dihydroartemisinin-piperaquine may also have an improved post-treatment prophylactic effect lasting for up to six weeks, and this effect may be present even when primaquine is also given to achieve radical cure (RR 0.21, 95% CI 0.10 to 0.46**, two trials, 179 participants, low quality evidence).The data available from low transmission settings is too limited to reliably assess the relative effectiveness of ACTs.

AUTHORS' CONCLUSIONS: ACTs appear at least equivalent to chloroquine at effectively treating the blood stage of P. vivax infection. Even in areas where chloroquine remains effective, this finding may allow for simplified protocols for treating all forms of malaria with ACTs. In areas where chloroquine no longer cures the infection, ACTs offer an effective alternative.**Dihydroartemisinin-piperaquine is the most studied ACT. It may provide a longer period of post-treatment prophylaxis than artemether-lumefantrine or artesunate plus amodiaquine. This effect may be clinically important in high transmission settings whether primaquine is also given or not.**

J Infect Dis. 2013 Sep 1;208(5):801-12. doi: 10.1093/infdis/jit261. Epub 2013 Jun 12.

Gametocyte dynamics and the role of drugs in reducing the transmission potential of Plasmodium vivax.

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BACKGROUND: Designing interventions that will reduce transmission of vivax malaria requires knowledge of Plasmodium vivax gametocyte dynamics.

METHODS: We analyzed data from a randomized controlled trial in northwestern Thailand and 2 trials in Papua, Indonesia, to identify and compare risk factors for vivax gametocytemia at enrollment and following treatment.

RESULTS: A total of 492 patients with P. vivax infections from Thailand and 476 patients (162 with concurrent falciparum parasitemia) from Indonesia were evaluable. Also, 84.3% (415/492) and 66.6% (209/314) of patients with monoinfection were gametocytemic at enrollment, respectively. The ratio of gametocytemia to asexual parasitemia did not differ between acute and recurrent infections (P = .48 in Thailand, P = .08 in Indonesia). High asexual parasitemia was associated with an increased risk of gametocytemia during follow-up in both locations. **In Thailand, the cumulative incidence of gametocytemia between day 7 and day 42 following dihydroartemisinin + piperaquine (DHA + PIP) was 6.92% vs 29.1% following chloroquine (P < .001). In Indonesia, the incidence of gametocytemia was 33.6% following artesunate + amodiaquine (AS + AQ), 7.42% following artemether + lumefantrine, and 6.80% following DHA + PIP (P < .001 for DHA + PIP vs AS + AQ).**

CONCLUSIONS: P. vivax gametocyte carriage mirrors asexual-stage infection. Prevention of relapses, particularly in those with high asexual parasitemia, is likely the most important strategy for interrupting P. vivax transmission.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23766527/

Malnutrition

(Papers listed in this section refer to the management of protein-energy malnutrition. For other relevant studies of nutrition see also Nutrition, Vitamin A, Vitamin D, Zinc, Maternal health, Anaemia and iron deficiency)

J Trop Pediatr. 2013 Oct;59(5):393-8. doi: 10.1093/tropej/fmt039. Epub 2013 Jun 10.

Effectiveness of indigenous ready-to-use therapeutic food in community-based management of uncomplicated severe acute malnutrition: a randomized controlled trial from India.

Randomised trials in child health in developing countries 2013-14

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A randomized controlled trial was conducted in Chandigarh, India (2011), to determine the effectiveness of indigenous ready-to-use therapeutic food (RUTF) in community-based management of uncomplicated severe acute malnutrition (SAM). Intervention was through outpatient therapeutic program site (OTP). Study and control group children (6 months-5 years) were followed up weekly for 12 weeks, in OTP and at home. **All children received supplementary nutrition through anganwadis under integrated child development scheme. Study children, in addition, received therapeutic dose of RUTF in OTP. Primary outcome, 115% of baseline weight, was attained in 6 of 13 (46.2%) and 1 of 13 (7.7%) children among study and control group, respectively [odds ratio: 10.28, 95% confidence interval (CI): 1.02-103.95].** Compared with control group, addition of RUTF in study group resulted in average additional increase in weight by 13 g/kg of baseline weight/week/child (95% CI: 2-23). Indigenous RUTF was effective in community-based management of uncomplicated SAM.

Nutr J. 2013 Aug 15;12:120. doi: 10.1186/1475-2891-12-120.

Acceptability and impact on anthropometry of a locally developed ready-to-use therapeutic food in pre-school children in Vietnam.

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BACKGROUND: In South East Asia, concerns exist about the acceptability of peanut-based Ready-to-Use-Therapeutic-Foods (RUTF) for the treatment of severe acute malnutrition (SAM). Therefore, an alternative, culturally acceptable RUTF made from locally available ingredients and complying with local food traditions and preferences was developed. The current study evaluated its acceptability and impact on anthropometry.

METHODS: The study was a randomized, two-arm, cross-over intervention trial to test the acceptability of the local product (bar) against a commercially available, peanut-based RUTF paste (Plumpy'nut). Children (n = 67) from two kindergartens in a rural area of North Vietnam were recruited. The age of the children was between 3 and 5 years.

RESULTS: The Vietnamese RUTF was well-accepted, although overall acceptability was less than of Plumpy'nut, with the latter scoring higher on palatability ($P < 0.05$). In contrast, reluctance to eat Plumpy'nut was higher than for the Vietnamese RUTF ($P < 0.05$). Impact on anthropmetrical indices was similar for both RUTF. The nutritional status of the children who consumed the two RUTF over a 4 week period improved significantly, with a mean weight gain of 0.64 (SD 0.27) Kg, and increases in WHZ and HAZ z-scores of 0.48 (SD 0.30) and 0.05 (SD 0.13) respectively ($P < 0.01$ both). Weight gain was similar between the 2 products (0.32 kg per 2 weeks for both).

CONCLUSIONS: Both the commercial Plumpy'nut and the local produced RUTF were accepted although the harder consistency of the local product might have caused the lower

overall acceptance. The promising increase in nutritional status needs to be confirmed in a controlled trial in children with SAM.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23945188/

Maternal health

PLoS One. 2013 Oct 22;8(10):e78162. doi: 10.1371/journal.pone.0078162. eCollection 2013.

Psychological and social factors associated with late pregnancy iron deficiency anaemia in rural Viet Nam: a population-based prospective study.

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OBJECTIVES: The aim of this study was to examine the relationships between psychological and social factors and late pregnancy IDA among pregnant women in rural Viet Nam.

METHODS: Pregnant women from 50 randomly-selected communes within Ha Nam province were recruited and assessed at 12 - 20 weeks gestation (Wave 1, W1). They were followed up in the last trimester (Wave 2, W2). IDA was defined as Haemoglobin < 11 g/dL and serum ferritin < 15 ng/mL. Symptoms of Common Mental Disorders (CMD) were assessed by the Edinburgh Postnatal Depression Scale-Vietnam (EPDS-V). Persistent antenatal CMD was defined as having an EPDS-V score ≥ 4 in both W1 and W2. Hypothesis models were tested by Structural Equation Modeling analyses.

RESULTS: A total of 378 women provided complete data at both W1 and W2. The incidence risk of IDA in the third trimester was 13.2% (95% confidence interval (CI): 9.8-16.7). Persistent CMD was found in 16.9% (95% CI: 13.1-20.7) pregnant women and predicted by intimate partner violence, fear of other family members, experience of childhood abuse, coincidental life adversity, and having a preference for the sex of the baby. There was a significant pathway from persistent CMD to IDA in late pregnancy via the length of time that iron supplements had been taken. Receiving advice to take iron supplements and higher household wealth index were indirectly related to lower risk of late pregnancy IDA. Early pregnancy IDA and being multi-parous also contributed to late pregnancy IDA.

CONCLUSIONS: Antenatal IDA and CMD are prevalent public health problems among women in Viet Nam. The link between them suggests that while direct recommendations to use iron supplements are important, the social factors associated with common mental disorders should be addressed in antenatal care in order to improve the health of pregnant women and their infants.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24167605/

Public Health Nutr. 2013 Aug;16(8):1354-61. doi: 10.1017/S1368980013000475. Epub 2013 Mar 7.

Plasma zinc, vitamin B(12) and α-tocopherol are positively and plasma γ-tocopherol is negatively associated with Hb concentration in early pregnancy in north-west Bangladesh.

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OBJECTIVE: The objective of the current analysis was to explore the association of multiple micronutrients with Hb concentration among pregnant women in a South Asian setting, a topic that has not been adequately explored.

DESIGN: Sociodemographic, anthropometric and micronutrient status (plasma ferritin, transferrin receptor, retinol, a- and g-tocopherol, folate, vitamin B12, Zn) and Hb concentration were assessed at early pregnancy.

SETTING: The biochemical sub-study was nested within a double-blind, placebo-controlled, community-based vitamin A and b-carotene supplementation trial in rural north-western Bangladesh (JiVitA). All assessments were conducted before trial supplementation was initiated.

SUBJECTS: A systematic sample of 285 women was selected from those enrolled in the biochemical sub study.

RESULTS: Seventeen per cent of women were mildly anaemic; moderate and severe anaemia was uncommon (2.1 %). a-Tocopherol, vitamin B12 and Zn deficiencies were common (43.5%, 19.7% and 14.7%, respectively); however, vitamin A, folate and Fe deficiencies were comparatively rare (7.4%, 2.8% and ,1%,respectively). Plasma Zn, vitamin B12 and a-tocopherol were positively associated and plasma g-tocopherol was negatively associated with Hb ($P < 0.05$) after adjustment for gestational age, inflammation status, season and nutritional status measured by mid-upper arm circumference.

CONCLUSIONS: **Among pregnant women in rural Bangladesh with minimal Fe deficiency, plasma Zn, vitamin B12, and a- and g-tocopherol concentrations were associated with Hb concentration.** Appreciating the influence on Hb of micronutrients in addition to those with known associations with anaemia, such as Fe, folate, and vitamin A, is important when addressing anaemia in similar settings.

Clin Infect Dis. 2014 Mar;58(5):651-9. doi: 10.1093/cid/cit806. Epub 2013 Dec 12.

Effectiveness of co-trimoxazole to prevent Plasmodium falciparum malaria in HIV-positive pregnant women in sub-Saharan Africa: an open-label, randomized controlled trial.

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BACKGROUND: Human immunodeficiency virus (HIV) and malaria during pregnancy cause substantial perinatal mortality. As co-trimoxazole (CMX) protects children and HIV-positive adults against malaria, we **compared the effectiveness of daily CMX with sulfadoxine-pyrimethamine intermittent preventive treatment (IPT-SP) on malaria risk in HIV-positive pregnant women in a Plasmodium falciparum-endemic African area**.

METHODS: From January 2009 to April 2011, we included in a randomized noninferiority trial all HIV type 1-infected pregnant women (≤28 weeks' gestation, CD4 count ≥200 cells/μL, hemoglobin level ≥7 g/L) in 19 health centers in Togo. Women were randomly assigned to daily 800 mg/160 mg CMX, or IPT-SP. **The primary outcome was the proportion of malaria-free pregnancies. Other outcomes included malaria incidence, parasitemia, placental malaria, anemia, and infants' birth weight.**

RESULTS: Of 264 women randomly assigned to the CMX or IPT-SP group, 126 of 132 and 124 of 132, respectively, were included in the analysis. **There were 33 confirmed cases of clinical malaria among 31 women in the CMX group, and 19 among 19 women in the IPT-SP group**. Ninety-five of 126 (75.4%) women in the CMX group and 105 of 124 (84.7%) in the IPT-SP group remained malaria-free during their pregnancy (difference, 9.3%; 95% confidence interval [CI], -.53 to 19.1, not meeting the predefined noninferiority criterion). **The incidence rate in intention-to-treat analysis was 108.8 malaria episodes per 100 person-years in CMX (95% CI, 105.4-112.2) and 90.1 in IPT-SP (95% CI, 86.8-93.4) (not significant).** Prevalence of parasitemia was 16.7% in the CMX group vs 28% in the IPT-SP group (P = .02). Histology revealed 20.3% placental malaria in the CMX group vs. 24.6% in the IPT-SP group (not significant). Grade 3-4 anemia was more frequent in the CMX group (10% vs 4%; P = .008). No pregnant women died. Median birth weight was similar.

CONCLUSIONS: Daily CMX was not noninferior to IPT-SP for preventing maternal malaria but safe and at least similar regarding parasitemia or placental malaria and birth outcomes. Clinical Trials Registration ISRCTN98835811.

Matern Child Health J. 2014 Jan;18(1):161-70. doi: 10.1007/s10995-013-1249-2.

Nutritional factors associated with antenatal depressive symptoms in the early stage of pregnancy among urban South Indian women.

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Many women of reproductive age from developing countries have poor nutritional status, and the prevalence of depression during pregnancy is high. **The objective of the present study was to assess the prevalence of antenatal depressive symptoms in early pregnancy**, and to identify the demographic and nutritional factors associated with these symptoms in a sample of urban South Indian pregnant women. This cross-sectional study was the baseline assessment of

a prospective randomized controlled trial of vitamin B12 supplementation in urban pregnant south Indian women between the ages of 18 and 40 years (www.clinicaltrials.gov : NCT00641862). 365 women in their first trimester of pregnancy were screened for depressive symptoms at an urban clinic in Karnataka, South India, using the Kessler Psychological Distress Scale (K-10). Nutritional, clinical and biochemical factors were also assessed. Mean (SD) age of the cohort was 22.6 (3.7) years and mean (SD) BMI was 20.4 (3.3) kg/m(2). 121 (33 %) of the women in the 1st trimester had symptoms consistent with depression (K-10 score >6). **In multivariate log binomial regression analysis, presence of antenatal depressive symptoms in the first trimester were positively associated with vomiting, prevalence ratio (PR) = 1.54 (95 % CI 1.10, 2.16) and negatively with anemia, PR = 0.67 (95 % CI 0.47, 0.96).** Nutrient intakes, serum vitamin B12, methylmalonic acid, homocysteine and red cell folate levels were not associated with measures of depression. Antenatal depressive symptoms in early pregnancy are highly prevalent in urban Indian women and are more common in women with vomiting and without anemia. In this cross-sectional data, blood concentrations of vitamin B12 and folate were not associated with depressive symptoms. The relationship between nutritional status and depressive symptoms may require larger and longitudinal studies.

Health Care Women Int. 2014;35(3):320-33. doi: 10.1080/07399332.2013.842240. Epub 2013 Nov 15.

The effect of planned baby care education given to primiparous mothers on maternal attachment and self-confidence levels.

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This study was conducted to examine the effect of planned baby care education on maternal attachment and self-confidence levels in primiparous mothers. The research was carried out using a pre-test, post-test, quasi-experimental design with a control group. In the intervention group, mothers were given planned baby care education and an education booklet. Both the median maternal attachment score and the mean self-confidence score increased by statistically significant levels in the intervention group, whereas there were no significant differences in the control group. It is recommended that primiparous mothers in particular should receive education regarding baby care.

J Nutr. 2013 Jul;143(7):1168-75. doi: 10.3945/jn.112.171751. Epub 2013 May 22.

Maternal weight loss during exclusive breastfeeding is associated with reduced weight and length gain in daughters of HIV-infected Malawian women.

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Maternal weight loss during exclusive breastfeeding may influence the growth of exclusively breast-fed infants through impaired quality or quantity of breast milk. **This study evaluated how maternal weight loss from 2 to 24 wk postpartum was related to infant weight and length gain in 1309 lactating HIV-infected mothers and their exclusively breast-fed infants**. Malawian mother-infant pairs in the Breastfeeding, Antiretrovirals, and Nutrition Study were randomized with a 2 × 3 factorial design to a 2-arm nutritional intervention with a lipid-based nutrient supplement (LNS), meeting nutritional needs of lactation, or no LNS and a 3-arm antiretroviral (ARV) intervention (maternal, infant, or no ARV regimen). **Linear regression models were used to relate maternal weight loss (weight loss vs. no weight loss) to infant weight and length gain from birth to 24 mo, stratifying by gender and controlling for maternal BMI at 2 wk (mean ± SD: 23.2 ± 3.0 kg/m(2)) and interacting maternal BMI with weight loss**. In adjusted models, compared with daughters of women who did not lose weight, length and weight gain were lower in daughters whose mothers had a lower BMI at 2 wk postpartum coupled with the weight loss. For example, among mothers with an initial BMI of 18 kg/m(2), daughters of those who lost weight gained less weight [β = -0.29 kg (95% CI: -0.53, -0.06)] and length [β = -0.88 cm (95% CI: -1.52, -0.23)] from birth to 24 wk than daughters of those who gained weight. Though effects were only observed in girls, suggesting possible gender differences in suckling and feeding behavior, these findings indicate that maternal weight loss with low energy reserves represents a risk factor for poor infant growth outcomes.

http://jn.nutrition.org/content/143/7/1168.full.pdf+html

BMC Pregnancy Childbirth. 2014 Jan 17;14:29. doi: 10.1186/1471-2393-14-29.

Mobile phones improve antenatal care attendance in Zanzibar: a cluster randomized controlled trial.

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BACKGROUND: Applying mobile phones in healthcare is increasingly prioritized to strengthen healthcare systems. Antenatal care has the potential to reduce maternal morbidity and improve newborns' survival but this benefit may not be realized in sub-Saharan Africa where the attendance and quality of care is declining. We evaluated the association between a mobile phone intervention and antenatal care in a resource-limited setting. We aimed to assess antenatal care in a comprehensive way taking into consideration utilisation of antenatal care as well as content and timing of interventions during pregnancy.

METHODS: This study was an open label pragmatic cluster-randomised controlled trial with primary healthcare facilities in Zanzibar as the unit of randomisation. **2550 pregnant women (1311 interventions and 1239 controls) who attended antenatal care at selected primary healthcare facilities were included at their first antenatal care visit and followed until 42 days after delivery.** 24 primary health care facilities in six districts were randomized to either mobile phone intervention or standard care. The intervention consisted of a **mobile phone text-message and voucher component.** Primary outcome measure was four or more antenatal care visits during pregnancy. Secondary outcome measures were tetanus vaccination, preventive treatment for malaria, gestational age at last antenatal care visit, and antepartum referral.

RESULTS: **The mobile phone intervention was associated with an increase in antenatal care attendance. In the intervention group 44% of the women received four or more antenatal care visits versus 31% in the control group (OR, 2.39; 95% CI, 1.03-5.55).** There was a trend towards improved timing and quality of antenatal care services across all secondary outcome measures although not statistically significant.

CONCLUSIONS: **The wired mothers' mobile phone intervention significantly increased the proportion of women receiving the recommended four antenatal care visits during pregnancy and there was a trend towards improved quality of care with more women receiving preventive health services,** more women attending antenatal care late in pregnancy and more women with antepartum complications identified and referred. Mobile phone applications may contribute towards improved maternal and newborn health and should be considered by policy makers in resource-limited settings.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24438517/

Maternal nutrition and micronutrient supplementation

Am J Clin Nutr. 2014 Jan;99(1):122-9. doi: 10.3945/ajcn.113.063404. Epub 2013 Oct 16.

Supplemental feeding during pregnancy compared with maternal supplementation during lactation does not affect schooling and cognitive development through late adolescence.

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BACKGROUND: The long-term impact of early malnutrition on human capital outcomes remains unclear, and existing evidence has come largely from observational studies.

OBJECTIVE: We compared the impact of a nutritional supplement given during pregnancy or lactation in rural Gambia on educational performance and cognitive ability in offspring at their maturity.

DESIGN: This study was a follow-up of a randomized trial of prenatal high protein and energy supplementation conducted between 1989 and 1994. Subjects were 16-22 y of age at follow-up, and information was collected on schooling achievement and cognitive ability by using the Raven's progressive matrices test, Mill Hill vocabulary test, and forward and backward digit-span tests.

RESULTS: **A total of 1459 individuals were traced and interviewed and represented 71% of the original cohort and 81% of the surviving cohort. There was no difference in cognitive ability or educational attainment between treatment groups by using any of the methods of assessment.**

CONCLUSION: We have shown little evidence to support a long-term effect of prenatal protein-energy supplementation compared with supplementation during lactation on cognitive development in rural Gambians. This trial was registered at http://www.controlled-trials.com as ISRCTN72582014.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24132979/

BMC Pregnancy Childbirth. 2014 Mar 20;14:111. doi: 10.1186/1471-2393-14-111.

Preconception maternal nutrition: a multi-site randomized controlled trial.

Hambidge KM[1], Krebs NF, Westcott JE, Garces A, Goudar SS, Kodkany BS, Pasha O, Tshefu A, Bose CL, Figueroa L, Goldenberg RL, Derman RJ, Friedman JE, Frank DN, McClure EM, Stolka K, Das A, Koso-Thomas M, Sundberg S; Preconception Trial Group.

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BACKGROUND: Research directed to optimizing maternal nutrition commencing prior to conception remains very limited, despite suggestive evidence of its importance in addition to ensuring an optimal nutrition environment in the periconceptional period and throughout the first trimester of pregnancy.

METHODS/STUDY DESIGN: This is an **individually randomized controlled trial of the impact on birth length (primary outcome) of the time at which a maternal nutrition intervention is commenced: Arm 1: ≥ 3 mo preconception vs. Arm 2: 12-14 wk gestation vs. Arm 3: none**.192 (derived from 480) randomized mothers and living offspring in each arm in each of four research sites (Guatemala, India, Pakistan, Democratic Republic of the Congo). **The intervention is a daily 20 g lipid-based (118 kcal) multi-micronutient (MMN) supplement.** Women randomized to receive this intervention with body mass index (BMI) <20 or whose gestational weight gain is low will receive an additional 300 kcal/d as a balanced energy-protein supplement. Researchers will visit homes biweekly to deliver intervention and monitor compliance, pregnancy status and morbidity; ensure prenatal and delivery care; and promote breast feeding. The primary outcome is birth length. Secondary outcomes include: fetal length at 12 and 34 wk; incidence of low birth weight (LBW); neonatal/infant anthropometry 0-6 mo of age; infectious disease morbidity; maternal, fetal, newborn, and infant epigenetics; maternal and infant nutritional status; maternal and infant microbiome; gut inflammatory biomarkers and bioactive and nutritive compounds in breast milk. The primary analysis will compare birth Length-for-Age Z-score (LAZ) among trial arms (independently for each site, estimated effect size: 0.35). Additional statistical analyses will examine the secondary outcomes and a pooled analysis of data from all sites.

DISCUSSION: Positive results of this trial will support a paradigm shift in attention to nutrition of all females of child-bearing age.

TRIAL REGISTRATION: ClinicalTrials.gov NCT01883193.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24650219/

Pediatrics. 2014 Apr;133(4):e1001-8. doi: 10.1542/peds.2013-2850. Epub 2014 Mar 3.

Prenatal nutrient supplementation and postnatal growth in a developing nation: an RCT.

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BACKGROUND AND OBJECTIVES: **Prenatal lipid-based nutrient supplements (LNS) have been shown to improve birth anthropometry**. However, little is known about the effects of such supplements on infant health. We hypothesized that prenatal LNS compared with multiple micronutrient supplement for pregnant and lactating women would improve survival, growth, and morbidity during infancy.

METHODS: **Infants' weight, length, head, chest, and mid-upper arm circumferences were measured during monthly home visits from birth to 12 months of age in the Micronutriments et Santé de la Mère et de l'Enfant--2 trial.** Differences in stunting and wasting episodes between study arms were assessed by Cox regression for recurrent event models. Morbidity signs during the 2 weeks before the visits and death cases were also assessed by multilevel analysis accounting for repeated individual measurements.

RESULTS: **Infant length-for-age growth (-0.033 z score/month; 95% confidence interval: -0.601 to -0.006; P = .018) for the LNS group was inferior to that of the control group. We did not find evidence of significant difference in mortality or morbidity between groups.**

CONCLUSIONS: **The previously reported positive effect of prenatal LNS on birth length was not sustained during the postnatal phase.** Prenatal LNS does not appear to make a long-lasting difference in child linear growth.

Am J Clin Nutr. 2013 Oct;98(4):972-82. doi: 10.3945/ajcn.113.059923. Epub 2013 Sep 4.

Randomized, placebo-controlled, calcium supplementation trial in pregnant Gambian women accustomed to a low calcium intake: effects on maternal blood pressure and infant growth.

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BACKGROUND: Dietary calcium intake in rural Gambian women is very low (~350 mg/d) compared with international recommendations. Studies have suggested that calcium supplementation of women receiving low-calcium diets significantly reduces risk of pregnancy hypertension.

OBJECTIVE: **We tested the effects on blood pressure (BP) of calcium carbonate supplementation (1500 mg Ca/d) in pregnant, rural Gambian women.**

DESIGN: The study was a **randomized, double-blind, parallel, placebo-controlled supplementation trial from 20 wk of gestation (P20) until delivery (calcium: n = 330; placebo; n = 332).** BP and anthropometric measures were taken at P20 and then 4 weekly until 36 wk of gestation (P36), and infant anthropometric measures were taken at 2, 13, and 52 wk postdelivery.

RESULTS: **A total of 525 (calcium: n = 260; placebo: n = 265) women had BP measured at P36 and subsequently delivered a healthy term singleton infant.** Mean compliance was 97%, and urinary calcium measures confirmed the group allocation. At P20, the mean (±SD) systolic blood pressure (SBP) was 101.2 ± 9.0 and 102.1 ± 9.3 mm Hg, and diastolic blood pressure (DBP) was 54.5 ± 7.3 and 55.8 ± 7.8 mm Hg, in the calcium and placebo groups, respectively. The intention-to-treat analysis that was adjusted for confounders showed no significant effect of calcium supplementation on the change between P20 and P36 (calcium compared with placebo; mean ± SEM) in SBP (-0.64 ± 0.65%; P = 0.3) or DBP (-0.22 ± 1.15%; P = 0.8). **There was no significant effect of supplementation on BP, pregnancy weight gain, weight postpartum, or infant weight, length, and other measures of growth.** However, the comparability of the original randomly assigned groups may have been compromised by the exclusion of 20.7% of women from the final analysis.

CONCLUSIONS: **Calcium supplementation did not affect BP in pregnancy.** This result may have been because the Gambian women were adapted to a low dietary calcium intake, and/or obesity, high gestational weight gain, high underlying BP, tobacco use, alcohol consumption, and sedentary lifestyles were rare. This trial was registered at the International Standard Randomized Controlled Trial Register (www.controlled-trials.com/mrct/) as ISRCTN96502494.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24004887/

J Pediatr. 2013 Dec;163(6):1605-1611.e3. doi: 10.1016/j.jpeds.2013.07.030. Epub 2013 Aug 30.

Maternal vitamin D3 supplementation during the third trimester of pregnancy: effects on infant growth in a longitudinal follow-up study in Bangladesh.

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OBJECTIVE: To estimate the effects of prenatal vitamin D supplementation on infant growth in Dhaka, Bangladesh.

STUDY DESIGN: **Longitudinal follow-up of infants born at term or late preterm (≥34 weeks) to participants in a randomized double-blind trial of maternal third-trimester vitamin D3 (35 000 IU/wk; vitamin D) vs placebo.** Anthropometry was performed at birth, 1, 2, 4, 6, 9, and 12 months of age. The primary analysis (n = 145 overall; n = 134 at 1 year) was a

comparison of mean length-for-age z-score (LAZ) based on World Health Organization standards.

RESULTS: **LAZ was similar between groups at birth, but 0.44 (95% CI, 0.06-0.82) higher in vitamin D vs placebo at 1 year, corresponding to a sex-adjusted increase of 1.1 cm (95% CI, 0.06-2.0).** Mean change in LAZ from birth to 1 month was significantly greater in vitamin D (0.53 per month) vs placebo (0.19 per month; P = .004); but there was no significant divergence thereafter. In longitudinal (repeated-measures) analysis, average LAZ during infancy was 0.41 higher in vitamin D vs placebo (95% CI, 0.11-0.71, P = .01). Stunting was less common in vitamin D (17% of infants were ever stunted) vs placebo (31%; P = .049). Other anthropometric indices were similar between groups.

CONCLUSIONS: **Maternal vitamin D3 supplementation (35 000 IU/wk) during the third trimester of pregnancy enhanced early postnatal linear growth in a cohort of infants in Bangladesh.**

Am J Clin Nutr. 2014 Apr;99(4):950-6. doi: 10.3945/ajcn.113.073833. Epub 2014 Feb 5.

Plasma and breast-milk selenium in HIV-infected Malawian mothers are positively associated with infant selenium status but are not associated with maternal supplementation: results of the Breastfeeding, Antiretrovirals, and Nutrition study.

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BACKGROUND: Selenium is found in soils and is essential for human antioxidant defense and immune function. In Malawi, low soil selenium and dietary intakes coupled with low plasma selenium concentrations in HIV infection could have negative consequences for the health of HIV-infected mothers and their exclusively breastfed infants.

OBJECTIVE: We tested the effects of lipid-based nutrient supplements (LNS) that contained 1.3 times the Recommended Dietary Allowance of sodium selenite and antiretroviral drugs (ARV) on maternal plasma and breast-milk selenium concentrations.

DESIGN: HIV-infected Malawian mothers in the Breastfeeding, Antiretrovirals, and Nutrition study were randomly assigned at delivery to receive: LNS, ARV, LNS and ARV, or a control. In a subsample of 526 mothers and their uninfected infants, we measured plasma and breast-milk selenium concentrations at 2 or 6 (depending on the availability of infant samples) and 24 wk postpartum.

RESULTS: Overall, mean (± SD) maternal (range: 81.2 ± 20.4 to 86.2 ± 19.9 μg/L) and infant (55.6 ± 16.3 to 61.0 ± 15.4 μg/L) plasma selenium concentrations increased, whereas breast-milk selenium concentrations declined (14.3 ± 11.5 to 9.8 ± 7.3 μg/L) from 2 or 6 to 24 wk postpartum (all $P < 0.001$). Compared with the highest baseline selenium tertile, low and middle tertiles were positively associated with a change in maternal plasma or breast-milk selenium from 2 or 6 to 24 wk postpartum (both $P < 0.001$). With the use of linear regression, we showed that LNS that contained selenium and ARV were not associated with changes in maternal plasma and breast-milk selenium, but maternal selenium concentrations were positively associated with infant plasma selenium at 2 or 6 and 24 wk postpartum ($P < 0.001$) regardless of the study arm.

CONCLUSIONS: **Selenite supplementation of HIV-infected Malawian women was not associated with a change in their plasma or breast-milk selenium concentrations.** Future research should examine effects of more readily incorporated forms of selenium (ie, selenomethionine) in HIV-infected breastfeeding women.

Measles

Cochrane Database Syst Rev. 2013 Aug 14;8:CD001477. doi: 10.1002/14651858.CD001477.pub4.

Antibiotics for preventing complications in children with measles.

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BACKGROUND: Measles is the leading killer among vaccine-preventable diseases; it is responsible for an estimated 44% of the 1.7 million vaccine-preventable deaths among children annually.
OBJECTIVES: To assess the effects of antibiotics given to children with measles to prevent complications and reduce pneumonia, other morbidities and mortality.

SEARCH METHODS: We searched CENTRAL 2013, Issue 4, MEDLINE (1966 to May week 4, 2013) and EMBASE (1980 to May 2013).

SELECTION CRITERIA: Randomised controlled trials (RCTs) and quasi-RCTs comparing antibiotics with placebo or no treatment, to prevent complications in children with measles.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted data and assessed trial quality.

MAIN RESULTS: Seven trials with 1263 children were included. The methodological quality of most studies was poor. Only two studies were randomized, double-blind trials. There was variation in antibiotics used, their doses, schedule and evaluation of outcome. Pooled study data showed that the incidence of pneumonia was lower in the treatment group compared to the

control group. However, the difference was not statistically significant. **Of the 654 children who received antibiotics, 27 (4.1%) developed pneumonia; while out of 609 children in the control group, 59 (9.6%) developed pneumonia (odds ratio (OR) 0.35; 95% confidence interval (0.12 to 1.01).** The one trial that showed an increase in the rate of pneumonia with antibiotics was conducted in 1942 and compared oral sulfathiazole with symptomatic treatment. If the results of this trial are removed from the meta-analysis, there is a statistically significant reduction in the incidence of pneumonia in children receiving antibiotics (OR 0.26; 95% CI 0.12 to 0.60). The incidence of other complications was significantly lower in children receiving antibiotics: purulent otitis media (OR 0.34; 95% CI 0.16 to 0.73) and tonsillitis (OR 0.08; 95% CI 0.01 to 0.72). There was no difference in the incidence of conjunctivitis (OR 0.39; 95% CI 0.15 to 1.0), diarrhea (OR 0.53; 95% CI 0.23 to 1.22) or croup (OR 0.16; 95% CI 0.01 to 4.06). No major adverse effects attributable to antibiotics were reported.

AUTHORS' CONCLUSIONS: The studies reviewed were of poor quality and used older antibiotics. **This review suggests a beneficial effect of antibiotics in preventing complications such as pneumonia, purulent otitis media and tonsillitis in children with measles**. On the basis of this review, it is not possible to recommend definitive guidelines on the type of antibiotic, duration or the day of initiation. There is a need for more evidence from high-quality RCTs to answer these questions.

Update of Cochrane Database Syst Rev. 2008;(3):CD001477.

http://onlinelibrary.wiley.com/store/10.1002/14651858.CD001477.pub4/asset/CD001477.pdf?v=1&t=hxd38ck9&s=ce39570c7b448c33584ba870925859cd408f27be

Neonatal care

Community Dent Oral Epidemiol. 2013 Aug;41(4):317-26. doi: 10.1111/cdoe.12030. Epub 2012 Dec 13.

Advising mothers about breastfeeding and weaning reduced pacifier use in the first year of life: a randomized trial.

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OBJECTIVE: To assess the effectiveness of home visits for advising mothers about breastfeeding and weaning on pacifier use in the first year of life.

METHOD: A randomized field trial was conducted on mothers who gave birth within the public health system in the Brazilian city of Sao Leopoldo (intervention group = 200; controls = 300). **The intervention group received the advice 10 days after the child's birth, monthly up to 6 months, at 8, 10, and 12 months, based on the 'Ten Steps for Healthy Feeding', a Brazilian national health policy for primary care, which follows WHO guidelines**. Relative risk (RR) was used to estimate the effects of the intervention on the risk of using a pacifier.

RESULTS: **55.4% of the children in the intervention group and 66.1% of the controls used a pacifier in the first year of life**. **The risk of using a pacifier was 16% lower for the intervention group (RR = 0.84; 95% CI, 0.71-0.99).** A multivariable Poisson regression

model showed higher adjusted risk of using a pacifier for children who had breastfeeding interrupted in the first month of life (RR = 1.43; 95% CI, 1.21-1.69) and whose mothers presented higher level of depression (RR = 1.40; 95% CI, 1.17-1.66).

CONCLUSIONS: Pacifier use is highly prevalent in the population studied. The home visits for dietary advice appear to help in reducing pacifier use in infants. These findings suggest the need for public health strategies that address early advice on pacifier use to promote child oral and general health.

Int J Nurs Stud. 2013 Dec;50(12):1689-97. doi: 10.1016/j.ijnurstu.2013.05.001. Epub 2013 Jun 2.

The effectiveness of a Chinese midwives' antenatal clinic service on childbirth outcomes for primipare: a randomised controlled trial.

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BACKGROUND: Antenatal care is an important component of maternity care. In many parts of the world, midwives are the primary caregivers for childbearing women, providing a high level of continuity of care during a normal pregnancy. While in China, obstetricians are the primary providers of antenatal care for all childbearing women; and midwives only provide intrapartum care to labouring women. Today midwifery as a profession in China has been marginalised. Pregnant women usually lack individualised continuity of care from midwives during the perinatal period. There have been few randomised controlled trials of midwifery care practice in mainland China.

OBJECTIVE: (1) To develop and implement a model of Chinese midwives' antenatal clinic service and (2) to explore its effect on childbirth outcomes, psychological state and satisfaction, for primiparae.

DESIGN AND METHODS: Two-group randomised controlled trial. One hundred and ten pregnant women were assessed for eligibility and invited to participate in either the intervention group (midwives' antenatal clinic service) or the control group (routine antenatal care) in the Obstetrics and Gynaecology Hospital of Fudan University from September 2011 to December 2011. Baseline data were collected, and then **women were randomised to individual midwives' antenatal clinic care (intervention group) or regular antenatal clinic service by obstetricians and obstetric nurse (control group). The research hypothesis was that compared with regular obstetrician-led antenatal care, the midwives' antenatal clinic service would decrease the caesarean section rate, produce more favourable birth outcomes and women's greater satisfaction with care.** Data were collected by retrospective review of case records and self-report questionnaires. The sample size of 110 was calculated to identify a decrease in caesarean birth from 70% to 40%. Birth outcomes, satisfaction and anxiety score in the two groups were compared.

SETTING: The midwives' antenatal clinic in the Obstetrics and Gynaecology Hospital of Fudan University, Shanghai, China.

PARTICIPANTS:
55 women, attending the midwives' antenatal clinic (the intervention group) and 55 women, entering the control group.

RESULTS: **Women in the intervention group were more likely than women in the control group to have a vaginal birth (35 [66.04%] versus 23 [43.40%]; 95% CI for difference 3.69-41.60).** Women in the intervention group had a higher perinatal satisfaction but lower anxiety score than those in the control group. No differences were seen in neonatal Apgar score and in the amount of bleeding 2h post partum.

CONCLUSION AND IMPLICATIONS FOR PRACTICE:
The midwives' antenatal clinic can decrease the rate of caesarean section and enhance women's satisfaction with midwifery care. Further research needs to be conducted to implement this model of care more widely. We will attempt to make midwifery care a true choice for Chinese women.

http://linkinghub.elsevier.com/retrieve/pii/S0020-7489(13)00142-9

Women Birth. 2014 Mar;27(1):37-40. doi: 10.1016/j.wombi.2013.09.004. Epub 2013 Nov 9.

Effect of immediate and continuous mother-infant skin-to-skin contact on breastfeeding self-efficacy of primiparous women: a randomised control trial.

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OBJECTIVE: To evaluate the effect of mother-infant immediate skin-to-skin contact on primiparous mother's breastfeeding self-efficacy.

STUDY DESIGN: A randomised control trial

SETTINGS: The study was conducted in Omolbanin obstetrics hospital (large tertiary hospital), Mashhad, Iran.

PARTICIPANTS: 114 18-35 year-old primiparous, Iranian, healthy and full term mothers who anticipated normal vaginal delivery and intended to breastfeed their babies.

INTERVENTION: Skin-to-skin contact immediately after birth and then controlling breastfeeding self-efficacy at 28 days postpartum.

MAIN OUTCOME MEASURE: Maternal breastfeeding self-efficacy at 28 days postpartum and success in first breastfeeding and mean time of first breastfeeding initiation.

RESULTS: **A total of 92 mother-infant dyads (47 dyads in skin-to-skin care skin-to-skin contact group and 45 dyads in routine care group)** were monitored and analysed. **In skin-to-skin contact group, breastfeeding self-efficacy was 53.42±8.57 SD as compared to 49.85±5.50 SD in routine care group which is significantly higher in skin-to-skin contact group (p=0.0003). Successful breastfeeding initiation rate was 56.6% in skin-to-skin contact group as compared to 35.6% in routine care group (p=0.02).** Time to initiate first feed was 21.98±9.10 SD min in SSC group vs. 66.55±20.76 min in routine care group (p<0.001).

CONCLUSION:
Mother-infant immediate skin-to-skin contact is an easy and available method of enhancing maternal breastfeeding self-efficacy. High breastfeeding self-efficacy increases exclusive breastfeeding duration.

http://linkinghub.elsevier.com/retrieve/pii/S1871-5192(13)00401-0

J Epidemiol Community Health. 2013 Dec 1;67(12):986-91. doi: 10.1136/jech-2013-202646. Epub 2013 Jul 19.

Sex differences in neonatal mortality in Sarlahi, Nepal: the role of biology and environment.

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BACKGROUND: Studies in South Asia have documented increased risk of neonatal mortality among girls, despite evidence of a biological survival advantage. Associations between gender preference and mortality are cited as reasons for excess mortality among girls. This has not, however, been tested in statistical models.
METHODS: A secondary analysis of data from a population-based randomised controlled trial of newborn infection prevention conducted in rural southern Nepal was used to estimate sex differences in early and late neonatal mortality, with girls as the reference group. The analysis investigated which underlying biological factors (immutable factors specific to the newborn or his/her mother) and environmental factors (mutable external factors) might explain observed sex differences in mortality.

RESULTS: Neonatal mortality was comparable by sex (Ref=girls; OR 1.06, 95% CI 0.92 to 1.22). **When stratified by neonatal period, boys were at 20% (OR 1.20, 95% CI 1.02% to 1.42%) greater risk of early and girls at 43% (OR 0.70, 95% CI 0.51% to 0.94%) greater risk of late neonatal mortality. Biological factors, primarily respiratory depression and unconsciousness at birth, explained excess early neonatal mortality among boys.** Increased late neonatal mortality among girls was explained by a three-way environmental interaction between ethnicity, sex and prior sibling composition (categorised as primiparous newborns, infants born to families with prior living boys or boys and girls, and infants born to families with only prior living girls).

CONCLUSIONS: Risk of neonatal mortality inverted between the early and late neonatal periods. Excess risk of early neonatal death among boys was consistent with biological expectations. Excess risk for late neonatal death among girls was not explained by overarching gender preference or preferential care-seeking for boys as hypothesised, but was driven by increased risk among Madeshi girls born to families with only prior girls.

Indian Pediatr. 2013 Aug;50(8):753-7. Epub 2012 Dec 5.

Phenobarbitone versus phenytoin for treatment of neonatal seizures: an open-label randomized controlled trial.

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OBJECTIVE: To compare the efficacy of phenobarbitone and phenytoin for treatment of neonatal seizures in term and near-term neonates.

DESIGN: Open labeled randomized controlled trial.

SETTING: Neonatal intensive care unit of a level II unit from India, from November 2008 to September 2009.

PARTICIPANTS: All term and late pre-term neonates admitted with clinically apparent seizures and not having any transient metabolic disorders (hypoglycemia or hypocalcemia) were randomly assigned.

INTERVENTION: **Phenobarbitone (n=54) or phenytoin (n=55) intravenously 20 mg/kg/dose over 20-30 min.** Neonates whose seizures were not controlled by the assigned drug were then crossed over to be treated with other drug in same dose.

PRIMARY OUTCOME VARIABLE: Clinical control of seizures (seizure free period of 24 hours after giving anticonvulsant).

RESULTS: Baseline characteristics including mean birthweight, gestation age and sex were comparable in both groups. **Seizures were controlled in 8 of the 55 (14.5%) neonates who received phenytoin, as compared to 39 of 54 (72.2%) neonates who received phenobarbitone (P <0.001).** In babies not responding to assigned drugs, after cross-over to the other drug, seizure control was achieved in 44/55 (80%) of the neonates assigned to receive phenytoin first as compared to 49/54 (91%) of those assigned to receive phenobarbitone first (P=0.014). After maximum dose of phenobarbitone seizures were controlled in 49/55(89%) in phenytoin group and 52/54 (96%) in phenobarbitone group (P<0.05).

CONCLUSIONS: **Phenobarbitone is more efficacious than phenytoin in control of clinical seizures in term or near-term neonates, irrespective of etiology**.

Anticonvulsants for neonates: high time we were seized of the matter. [Indian Pediatr. 2013]

Neonatal seizures: continued debate on phenobarbitone versus phenytoin. [Indian Pediatr. 2013]

http://www.indianpediatrics.net/aug2013/753.pdf

Low birth weight and prematurity

Indian Pediatr. 2014 May 8;51(5):367-70.

Glycerin suppository for promoting feeding tolerance in preterm very low birthweight neonates: a randomized controlled trial.

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OBJECTIVE: To compare the efficacy of glycerin suppository versus no suppository in preterm very-low-birthweight neonates for improving feeding tolerance.

DESIGN: Randomized controlled trial.

SETTING: Level III neonatal unit from Mumbai, India.

PARTICIPANTS:
50 very-low-birthweight (birth weight between 1000 to 1500 grams) preterm (gestational age between 28 to 32 weeks) neonates randomized to glycerine suppository (n=25) or no intervention (n=26).

INTERVENTION: Glycerin suppository (1g) once a day from day-2 to day-14 of life or no suppository, along with intermittent oral feeds and standardized care.

PRIMARY OUTCOME: Time required to achieve full enteral feeds (180 mL/kg/d).

RESULTS: Baseline characteristics of neonates like gestational age, birthweight, gender and age at the time of introduction of feeds were comparable in both groups. **The mean (SD) duration to reach full enteral feed was 11.90 (3.1) days in glycerin suppository group and was not significantly different (P=0.58) from control group, [11.33 (3.57) days].** Glycerin suppository group regained birth weight 2 days earlier than control group but this difference was not significant (P=0.16). There was no significant difference in duration of hospital stay or occurrence of necrotizing enterocolitis amongst the two study groups.

CONCLUSIONS: **Once daily application of glycerin suppository does not accelerate the achievement of full feeds in preterm very-low-birthweight neonates.**

Arch Dis Child Fetal Neonatal Ed. 2014 Mar;99(2):F105-9. doi: 10.1136/archdischild-2013-304650. Epub 2013 Dec 3.

Early versus late enteral prophylactic iron supplementation in preterm very low birth weight infants: a randomised controlled trial.

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OBJECTIVES: To evaluate whether preterm very low birth weight (VLBW) infants receiving early iron (EI) supplementation (2 mg/kg/day elemental iron) at 2 weeks postnatal age have improved serum ferritin levels compared with late iron (LI) supplementation at 6 weeks postnatal age.

DESIGN: Single-blinded parallel-group interventional randomised controlled trial.

SETTING: Tertiary care centre in southern India.

INTERVENTIONS: Randomised at 2 weeks postnatal age to EI and LI groups and evaluated at 2, 6 and 12 weeks postnatal age.

OUTCOME: The primary outcome was serum ferritin level at 12 weeks, and the secondary outcomes were the incidence of neonatal morbidities, haemoglobin level, anthropometric parameters and blood transfusion requirements.

RESULTS: Of the 104 babies randomised, outcomes were analysed in 46 and 47 babies in EI and LI groups, respectively. **Serum ferritin level was significantly higher ($p<0.001$) at 12 weeks (82±5 vs 63±3 ng/mL) in the EI group**. Haemoglobin (10.1±0.4 vs 9.2±0.4 g/dL) and mean corpuscular haemoglobin concentration (31±0.5 vs 29.4±0.5 g/dL) were also significantly ($p<0.001$) higher at 12 weeks in the EI group. There was a significant decrease of ferritin in the LI group and significant increase in ferritin in the EI group at 6 weeks compared with 2 weeks. There were no significant differences in the incidences of neonatal morbidities (necrotising enterocolitis, periventricular leukomalacia, retinopathy of prematurity), anthropometric parameters and blood transfusion requirements between the two groups.

CONCLUSIONS: EI supplementation in preterm VLBW infants improves serum ferritin and haemoglobin levels.

PLoS One. 2014 Mar 3;9(3):e90128. doi: 10.1371/journal.pone.0090128.

Factors associated with preterm, early preterm and late preterm birth in Malawi.

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BACKGROUND:
Assessment of risk factors for preterm birth in a population with high incidence of preterm birth and HIV infection.

METHODS: Secondary analysis of data for 2,149 women included in a community based randomized placebo controlled trial for the prevention of preterm birth (APPLe trial (ISRCTN84023116) with gestational age at birth determined through ultrasound measurement in early pregnancy. Multivariate Logistic Regression analyses to obtain models for three outcome variables: all preterm, early preterm, and late preterm birth.

FINDINGS: **No statistical differences were noted for the prevalence of HIV infection (p=0.30) or syphilis (p=0.12) between women who delivered preterm versus term**. BMI (Adjusted OR 0.91 (0.85-0.97); p=0.005) and weight gain (Adjusted OR 0.89 (0.82-0.97); p=0.006) had an independent, protective effect. Previous preterm birth doubled the odds of preterm birth (Adjusted OR 2.13 (1.198-3.80); p=0.01). Persistent malaria (despite malaria prophylaxis) increased the risk of late preterm birth (Adjusted OR 1.99 (1.05-3.79); p=0.04). Age <20 (Adjusted OR 1.73 (1.03-2.90); p=0.04) and anemia (Adjusted OR 1.95 (1.08-3.52); p=0.03) were associated with early preterm birth (<34 weeks).

CONCLUSIONS: **Despite claims that HIV infection is an important cause of preterm birth in Africa, we found no evidence of an association in this population (unexposed to anti-retroviral treatment).** Persistent malaria was associated with late preterm birth. Maternal undernourishment and anemia were independently associated with early preterm birth. The study did not assess whether the link was direct or whether a common precursor such as chronic infection was responsible for both maternal effects and early labour.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24595186/

Pediatr Cardiol. 2014 Jun;35(5):824-30. doi: 10.1007/s00246-014-0861-2. Epub 2014 Jan 17.

Comparison of oral ibuprofen with oral indomethacin for PDA closure in Indian preterm neonates: a randomized controlled trial.

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Oral ibuprofen is being used as an alternative to indomethacin in medical management of patent ductus arteriosus (PDA), but limited data exist on oral efficacy of these drugs for PDA closure in India. **To assess and compare the efficacy of oral ibuprofen and oral indomethacin for PDA closure in preterm Indian neonates, we designed a randomized controlled study on clinically diagnosed and echocardiographically confirmed hemodynamically significant PDA in preterm neonates. Patients were assigned to receive either oral ibuprofen at a dosage of 10, 5, 5 mg/kg every 24 h or three doses of oral indomethacin (0.20-0.25 mg/kg every 24 h) starting on the third day of life or when diagnosed. A second course of ibuprofen/indomethacin was given, if PDA failed to close within 48 h after the first course.** Patients were monitored for complications like oliguria, bleeding, necrotizing enterocolitis, intraventricular hemorrhage, oxygen dependency, and gastrointestinal side effects. The baseline characteristics were comparable in both groups. Of the 83 children enrolled, 57.8 % received oral ibuprofen and 42.1 % received oral indomethacin. **The overall closure rate of PDA was 60**

and 65.7 % in the ibuprofen and indomethacin groups, respectively. **Closure rate was significantly higher when the drugs were administered at an early postnatal age (<8 days) (83.3 % [p = 0.02] in the indomethacin group and 75 % [p = 0.03] in the ibuprofen group) in neonates >28 weeks (ibuprofen group 66.7 % [p = 0.02]; indomethacin group 65.5 % [p = 0.04]) and in babies with birth weight >1,000 g (ibuprofen group 62.2 %; indomethacin group 70 % [p = 0.04 in both groups]).** Complications were similar in both groups. The efficacy of both drugs was similar. Poor closure in our study could be because of genetic differences in pharmacokinetics of drug metabolism in the Indian population. Regimens with higher doses or increased duration of treatment may increase the frequency of closure. Studies with larger numbers of subjects with evaluation of pharmacokinetic parameters are therefore required.

Nutrition. 2014 Jun;30(6):645-53. doi: 10.1016/j.nut.2013.10.024. Epub 2013 Nov 5.

Probiotics, feeding tolerance, and growth: a comparison between HIV-exposed and unexposed very low birth weight infants.

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OBJECTIVE: The aim of this study was to compare the effect of administration of probiotics on feeding tolerance and growth outcomes of HIV-exposed (but uninfected) versus HIV non-exposed preterm infants. The null hypothesis of this study states that there will be no difference in the feeding tolerance and growth outcomes for both probiotic-exposed and unexposed premature very low birth weight infants.

METHODS: **A randomized, double-blind, placebo-controlled trial was conducted during the period from July 2011 to August 2012. HIV-exposed and non-exposed premature (<34 wk gestation) infants with a birth weight of ≥500 g and ≤1250 g were randomized to receive either a probiotic mixture or placebo.** The multispecies probiotic mixture consisted of 1 × 10(9) CFU, Lactobacillus rhamnosus GG and Bifidobacterium infantis per day and was administered for 28 d. Anthropometrical parameters, daily intakes, and feeding tolerance were monitored.

RESULTS: Seventy-four HIV-exposed and 110 unexposed infants were enrolled and randomized (mean birth weight 987 g ± 160 g, range, 560-1244 g; mean gestational age 28.7 wk). In all 4227 probiotic doses were administered (mean 22.9/infant). **There was no difference in the average daily weight gain for treatment groups or HIV exposure.** The HIV-exposed group achieved significantly higher z scores for length and head circumference at day 28 than the unexposed group (P < 0.01 and P = 0.03, respectively). There were no differences in the incidence of any signs of feeding intolerance and abdominal distension between the groups.

CONCLUSION: **Probiotic supplementation did not affect growth outcomes or the incidence of any signs of feeding intolerance in HIV exposure.**

Neonatal sepsis

Pediatr Infect Dis J. 2013 Sep;32 Suppl 1:S19-25. doi: 10.1097/INF.0b013e31829ff7aa.

Simplified antibiotic regimens for the management of clinically diagnosed severe infections in newborns and young infants in first-level facilities in Karachi, Pakistan: study design for an outpatient randomized controlled equivalence trial.

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BACKGROUND: Infection in young infants is a major cause of morbidity and mortality in low-middle income countries, with high neonatal mortality rates. Timely case management is lifesaving, but the current standard of hospitalization for parenteral antibiotic therapy is not always feasible. Alternative, simpler antibiotic regimens that could be used in outpatient settings have the potential to save thousands of lives.

METHODS: This trial aims to determine whether 2 simplified antibiotic regimens are equivalent to the reference therapy with 7 days of once-daily (OD) intramuscular (IM) procaine penicillin and gentamicin for outpatient management of young infants with clinically presumed systemic bacterial infection treated in primary health-care clinics in 5 communities in Karachi, Pakistan. The reference regimen is close to the current recommendation of the hospital-based intravenous ampicillin and gentamicin therapy for neonatal sepsis. **The 2 comparison arms are (1) IM gentamicin OD and oral amoxicillin twice daily for 7 days; and (2) IM penicillin and gentamicin OD for 2 days, followed by oral amoxicillin twice daily for 5 days**; 2250 "evaluable" infants will be enrolled. The primary outcome of this trial is treatment failure (death, deterioration or lack of improvement) within 7 days of enrollment. Results are expected by early 2014.

DISCUSSION: **This trial will determine whether simplified antibiotic regimens with fewer injections in combination with high-dose amoxicillin are equivalent to 7 days of IM procaine penicillin and gentamicin in young infants with clinical severe infection**. Results will have program and policy implications in countries with limited access to hospital care and high burden of neonatal deaths.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23945571/

Nutrition, micronutrients and breast feeding

(see also Anaemia and iron deficiency, Zinc, Maternal nutrition, Vitamin A, Tuberculosis, Helminths and other gastrointestinal infections, HIV case management)

Micronutients and food fortification

Lancet. 2013 Jul 6;382(9886):29-40. doi: 10.1016/S0140-6736(13)60437-7. Epub 2013 Apr 18.

Effect of provision of daily zinc and iron with several micronutrients on growth and morbidity among young children in Pakistan: a cluster-randomised trial.

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BACKGROUND: Powders containing iron and other micronutrients are recommended as a strategy to prevent nutritional anaemia and other micronutrient deficiencies in children. **We assessed the effects of provision of two micronutrient powder formulations, with or without zinc, to children in Pakistan.**

METHODS: We did a cluster randomised trial in urban and rural sites in Sindh, Pakistan. A baseline survey identified 256 clusters, which were randomly assigned (within urban and rural strata, by computer-generated random numbers) to one of three groups: **non-supplemented control (group A), micronutrient powder without zinc (group B), or micronutrient powder with 10 mg zinc (group C)**. Children in the clusters aged 6 months were eligible for inclusion in the study. Powders were to be given daily between 6 and 18 months of age; follow-up was to age 2 years. Micronutrient powder sachets for groups B and C were identical except for colour; investigators and field and supervisory staff were masked to composition of the micronutrient powders until trial completion. Parents knew whether their child was receiving supplementation, but did not know whether the powder contained zinc. Primary outcomes were growth, episodes of diarrhoea, acute lower respiratory tract infection, fever, and incidence of admission to hospital. This trial is registered with ClinicalTrials.gov, number NCT00705445.

RESULTS: The trial was done between Nov 1, 2008, and Dec 31, 2011. **947 children were enrolled in group A clusters, 910 in group B clusters, and 889 in group C clusters. Micronutrient powder administration was associated with lower risk of iron-deficiency anaemia at 18 months compared with the control group (odds ratio [OR] for micronutrient powder without zinc=0·20, 95% CI 0·11-0·36; OR for micronutrient powder with zinc=0·25, 95% CI 0·14-0·44).** Compared with the control group, children in the group receiving micronutrient powder without zinc gained an extra 0·31 cm (95% CI 0·03-0·59) between 6 and 18 months of age and children receiving micronutrient powder with zinc an extra 0·56 cm (0·29-0·84). **We recorded strong evidence of an increased proportion of days with diarrhoea (p=0·001) and increased incidence of bloody diarrhoea (p=0·003) between 6 and 18 months in the two micronutrient powder groups, and reported chest indrawing**

(p=0·03). Incidence of febrile episodes or admission to hospital for diarrhoea, respiratory problems, or febrile episodes did not differ between the three groups.

INTERPRETATION: **Use of micronutrient powders reduces iron-deficiency anaemia in young children. However, the excess burden of diarrhoea and respiratory morbidities associated with micronutrient powder use and the very small effect on growth recorded suggest that a careful assessment of risks and benefits must be done in populations with malnourished children and high diarrhoea burdens.**

Ann N Y Acad Sci. 2014 Jan;1308:218-31. doi: 10.1111/nyas.12278. Epub 2013 Nov 8.

Integrating nutrition and early child-development interventions among infants and preschoolers in rural India.

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This article describes the development, design, and implementation of an integrated randomized double-masked placebo-controlled trial (Project Grow Smart) that examines how home/preschool fortification with multiple micronutrient powder (MNP) combined with an early child-development intervention affects child development, growth, and micronutrient status among infants and preschoolers in rural India. The 1-year trial has an infant phase (enrollment age: 6-12 months) and a preschool phase (enrollment age: 36-48 months). Infants are individually randomized into one of four groups: placebo, placebo plus early learning, MNP alone, and MNP plus early learning (integrated intervention), conducted through home visits. The preschool phase is a cluster-randomized trial conducted in Anganwadi centers (AWCs), government-run preschools sponsored by the Integrated Child Development System of India. AWCs are randomized into MNP or placebo, with the MNP or placebo mixed into the children's food. The evaluation examines whether the effects of the MNP intervention vary by the quality of the early learning opportunities and communication within the AWCs. Study outcomes include child development, growth, and micronutrient status. Lessons learned during the development, design, and implementation of the integrated trial can be used to guide large-scale policy and programs designed to promote the developmental, educational, and economic potential of children in developing countries.

J Nutr. 2013 Oct;143(10):1540-8. doi: 10.3945/jn.113.175018. Epub 2013 Aug 21.

The plasma proteome identifies expected and novel proteins correlated with micronutrient status in undernourished Nepalese children.

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Micronutrient deficiencies are common in undernourished societies yet remain inadequately assessed due to the complexity and costs of existing assays. A plasma proteomics-based

approach holds promise in quantifying multiple nutrient:protein associations that reflect biological function and nutritional status. To validate this concept, in plasma samples of a cohort of 500 6- to 8-y-old Nepalese children, we estimated cross-sectional correlations between vitamins A (retinol), D (25-hydroxyvitamin D), and E (α-tocopherol), copper, and selenium, measured by conventional assays, and relative abundance of their major plasma-bound proteins, measured by quantitative proteomics using 8-plex iTRAQ mass tags. The prevalence of low-to-deficient status was 8.8% (<0.70 μmol/L) for retinol, 19.2% (<50 nmol/L) for 25-hydroxyvitamin D, 17.6% (<9.3 μmol/L) for α-tocopherol, 0% (<10 μmol/L) for copper, and 13.6% (<0.6 μmol/L) for selenium. **We identified 4705 proteins, 982 in >50 children. Employing a linear mixed effects model, we observed the following correlations: retinol:retinol-binding protein 4 (r = 0.88), 25-hydroxyvitamin D:vitamin D-binding protein (r = 0.58), α-tocopherol:apolipoprotein C-III (r = 0.64), copper:ceruloplasmin (r = 0.65), and selenium:selenoprotein P isoform 1 (r = 0.79) (all P < 0.0001), passing a false discovery rate threshold of 1% (based on P value-derived q values).** Individual proteins explained 34-77% (R(2)) of variation in their respective nutrient concentration. Adding second proteins to models raised R(2) to 48-79%, demonstrating a potential to explain additional variation in nutrient concentration by this strategy. **Plasma proteomics can identify and quantify protein biomarkers of micronutrient status in undernourished children.** The maternal micronutrient supplementation trial, from which data were derived as a follow-up activity, was registered at clinicaltrials.gov as NCT00115271.

Am J Clin Nutr. 2013 Sep;98(3):731-7. doi: 10.3945/ajcn.113.059592. Epub 2013 Jul 31.

Folic acid and vitamin B-12 supplementation and common infections in 6-30-mo-old children in India: a randomized placebo-controlled trial.

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BACKGROUND: Young children in low- and middle-income countries frequently have inadequate vitamin B-12 (cobalamin) status. Poor folate status is also common and is associated with increased diarrheal and respiratory morbidity.

OBJECTIVE: The objective was to measure the effect of folic acid and/or vitamin B-12 administration on the incidence of diarrhea and acute lower respiratory tract infections.

DESIGN: **One thousand North Indian children (6-30 mo of age) were enrolled in a randomized, double-blind, placebo-controlled trial to receive 2 times the Recommended Dietary Allowance of folic acid and/or vitamin B-12 or placebo daily for 6 mo.** Children were individually randomly assigned in a 1:1:1:1 ratio in blocks of 16. Primary outcomes were the number of episodes of acute lower respiratory infections, diarrhea, and prolonged diarrhea.

RESULTS: Folic acid and vitamin B-12 supplementation significantly improved vitamin B-12 and folate status, respectively. **Neither folic acid nor vitamin B-12 administration reduced the incidence of diarrhea or lower respiratory infections. In comparison with placebo, children treated with folic acid alone or in combination with vitamin B-12 had a significantly higher risk of persistent diarrhea (OR: 2.1; 95% CI: 1.1, 3.8).**

CONCLUSIONS: Folic acid or vitamin B-12 supplementation did not reduce the burden of common childhood infections. In view of the increased risk of diarrhea, the safety of folic acid supplements in young children should be further assessed. This trial was registered at www.clinicaltrials.gov as NCT00717730 and at www.ctri.nic.in as CTRI/2010/091/001090.

J Nutr. 2013 Sep;143(9):1489-93. doi: 10.3945/jn.113.176677. Epub 2013 Jul 10.

Biofortification of pearl millet with iron and zinc in a randomized controlled trial increases absorption of these minerals above physiologic requirements in young children.

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Erratum in
J Nutr. 2013 Dec;143(12):2055.

Millet is unusually drought resistant and consequently there is a progressive increase in the use of these grains as a human food staple, especially in large areas of India and sub-Saharan Africa. The purpose of this study was to determine the absorption of iron and zinc from pearl millet biofortified with 2 micronutrients that are typically deficient in nonfortified, plant-based diets globally. **The study was undertaken in 40 children aged 2 y in Karnataka, India (n = 21 test/19 controls). Three test meals providing ~84 ± 17 g dry pearl millet flour were fed on a single day for zinc and 2 d for iron between 0900 and 1600 h. The quantities of zinc and iron absorbed were measured with established stable isotope extrinsic labeling techniques and analyses of duplicate diets. The mean (± SD) quantities of iron absorbed from test and control groups were 0.67 ± 0.48 and 0.23 ± 0.15 mg/d, respectively (P < 0.001).** The quantities of zinc absorbed were 0.95 ± 0.47 and 0.67 ± 0.24 mg/d, respectively (P = 0.03). These data did not include absorption of the modest quantities of iron and zinc contained in snacks eaten before and after the 3 test meals. **In conclusion, quantities of both iron and zinc absorbed when iron and zinc biofortified pearl millet is fed to children aged 2 y as the major food staple is more than adequate to meet the physiological requirements for these micronutrients.**

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23843474/

Br J Nutr. 2013 Dec;110(12):2271-84. doi: 10.1017/S000711451300189X. Epub 2013 Jul 4.

Effects of a multi-micronutrient-fortified beverage, with and without sugar, on growth and cognition in South African schoolchildren: a randomised, double-blind, controlled intervention.

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Little is known about the effects of combined micronutrient and sugar consumption on growth and cognition. In the present study, we investigated the effects of micronutrients and sugar,

alone and in combination, in a beverage on growth and cognition in schoolchildren. **In a 2 × 2 factorial design, children (n 414, 6-11 years) were randomly allocated to consume beverages containing (1) micronutrients with sugar, (2) micronutrients with a non-nutritive sweetener, (3) no micronutrients with sugar or (4) no micronutrients with a non-nutritive sweetener for 8.5 months.** Growth was assessed and cognition was tested using the Kaufman Assessment Battery for Children version II (KABC-II) subtests and the Hopkins Verbal Learning Test (HVLT). Micronutrients decreased the OR for Fe deficiency at the endpoint (OR 0.19; 95% CI 0.07, 0.53). Micronutrients increased KABC Atlantis (intervention effect: 0.76; 95% CI 0.10, 1.42) and HVLT Discrimination Index (1.00; 95% CI 0.01, 2.00) scores. Sugar increased KABC Atlantis (0.71; 95% CI 0.05, 1.37) and Rover (0.72; 95% CI 0.08, 1.35) scores and HVLT Recall 3 (0.94; 95% CI 0.15, 1.72). Significant micronutrient × sugar interaction effects on the Atlantis, Number recall, Rover and Discrimination Index scores indicated that **micronutrients and sugar in combination attenuated the beneficial effects of micronutrients** or sugar alone. Micronutrients or sugar alone had a lowering effect on weight-for-age z-scores relative to controls (micronutrients - 0.08; 95% CI - 0.15, - 0.01; sugar - 0.07; 95% CI - 0.14, - 0.002), but in combination, this effect was attenuated. The beverages with micronutrients or added sugar alone had a beneficial effect on cognition, which was attenuated when provided in combination.

Comment

An unusually designed study, it is hard to imagine what overall benefits could come from adding sugar to micronutrients (or to any other drugs). The long term effects on dental caries and obesity were not assessed in this study. There are already far too many sugar-rich beverages consumed by children!

J Nutr. 2013 Jul;143(7):1184-93. doi: 10.3945/jn.112.166397. Epub 2013 May 22.

Probiotics Lactobacillus reuteri DSM 17938 and Lactobacillus casei CRL 431 modestly increase growth, but not iron and zinc status, among Indonesian children aged 1-6 years.

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Probiotics and milk calcium may increase resistance to intestinal infection, but their effect on growth and iron and zinc status of Indonesian children is uncertain. We investigated the **hypotheses that cow milk with added probiotics would improve growth and iron and zinc status of Indonesian children, whereas milk calcium alone would improve growth but reduce iron and zinc status.** A 6-mo randomized trial was conducted in low-socioeconomic urban communities of Jakarta. Healthy children (n = 494) were randomly assigned to receive low-lactose milk with a low calcium content of ~50 mg/d (LC; n = 124), a regular calcium content of ~440 mg/d (RC group; n = 126), regular calcium with 5 × 10(8) CFU/d Lactobacillus casei CRL 431 (casei; n = 120), or regular calcium with 5 × 10(8) CFU/d Lactobacillus reuteri DSM 17938 (reuteri; n = 124). Growth, anemia, and iron and zinc status were assessed before and after the intervention. **Compared with the RC group, the reuteri group had significantly greater weight gain [0.22 (95% CI: 0.02, 0.42) kg], weight-for-age Z-score (WAZ) changes [0.09 (95% CI: 0.01, 0.17)], and monthly weight [0.03 (95% CI: 0.002, 0.05) kg/mo] and**

height [0.03 (95% CI: 0.01, 0.05) cm/mo] velocities. Casei significantly increased monthly weight velocity [0.03 (95% CI: 0.001, 0.05) kg/mo], but not height. However, the changes in underweight, stunting, anemia prevalence, and iron and zinc status were similar between groups. In conclusion, L. reuteri DSM 17938 modestly improved growth by increasing weight gain, WAZ changes, and weight and height velocity, whereas L. casei CRL 431 modestly improved weight velocity. Independent from probiotics supplementation, regular milk calcium did not affect growth or iron and zinc status.

http://jn.nutrition.org/cgi/pmidlookup?view=long&pmid=23700339

Breastfeeding

BMC Public Health. 2014 Jan 15;14:36. doi: 10.1186/1471-2458-14-36.

A complex breastfeeding promotion and support intervention in a developing country: study protocol for a randomized clinical trial.

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BACKGROUND: Breastfeeding has countless benefits to mothers, children and community at large, especially in developing countries. Studies from Lebanon report disappointingly low breastfeeding exclusivity and continuation rates. Evidence reveals that **antenatal breastfeeding education, professional lactation support, and peer lay support** are individually effective at increasing breastfeeding duration and exclusivity, particularly in low-income settings. Given the complex nature of the breastfeeding ecosystem and its barriers in Lebanon, we **hypothesize that a complex breastfeeding support intervention, which is centered on the three components mentioned above, would significantly increase breastfeeding rates.**

METHODS/DESIGN: A multi-center randomized controlled trial. Study population: 443 healthy pregnant women in their first trimester will be randomized to control or intervention group. Intervention: A "prenatal/postnatal" professional and peer breastfeeding support package continuing till 6 months postpartum, guided by the Social Network and Social Support Theory. Control group will receive standard prenatal and postnatal care. Mothers will be followed up from early pregnancy till five years after delivery. Outcome measures: Total and exclusive breastfeeding rates, quality of life at 1, 3 and 6 months postpartum, maternal breastfeeding knowledge and attitudes at 6 months postpartum, maternal exclusive breastfeeding rates of future infants up to five years from baseline, cost-benefit and cost-effectiveness analyses of the intervention. Statistical analysis: Descriptive and regression analysis will be conducted under the intention to treat basis using the most recent version of SPSS.

DISCUSSION: Exclusive breastfeeding is a cost-effective public health measure that has a significant impact on infant morbidity and mortality. In a country with limited healthcare resources like Lebanon, developing an effective breastfeeding promotion and support intervention that is easily replicated across various settings becomes a priority. If positive, the results of this study would provide a generalizable model to bolster breastfeeding promotion efforts and contribute to improved child health in Lebanon and the Middle East and North Africa (MENA) region.

TRIAL REGISTRATION: Current Controlled Trials ISRCTN17875591

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24428951/

Acta Paediatr. 2013 Aug;102(8):815-23. doi: 10.1111/apa.12282. Epub 2013 May 20.

Effects of exclusive breastfeeding intervention on child growth and body composition: the MINIMat trial, Bangladesh.

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AIM: Exclusive breastfeeding (EBF) for 6 months is recommended for optimal infant health, but the evidence for longer-term impacts is weak. **We examined whether randomization to receive EBF counselling (BFC) in rural Bangladeshi women had an impact on childhood growth trajectories and body composition.**

METHODS: In the Maternal and Infant Nutrition Interventions in Matlab trial, **4436 pregnant women were randomized to six equally sized, food and micronutrient groups. Of these, 3214 were randomized during the last trimester of pregnancy to receive either BFC or the usual/standard health message (UHM).** Their infants were extensively followed up, with anthropometric measurements between 0 and 54 months and assessment of body composition at 54 months.

RESULTS: **The mean duration of EBF in the BFC group was 111 days compared to 76 days in the UHM group (mean difference: 35.0 days, 95% CI 30.6-39.5, p < 0.001). There was no difference in growth trajectories between the BFC and UHM groups and no difference in body composition at 54 months. Children exposed to prenatal multiple micronutrients (vs 60 mg iron and folate) combined with BFC (vs UHM), however, had slower linear growth (mean difference -0.17 SD score, p < 0.01).**

CONCLUSION: Exclusive breastfeeding counselling resulted in neither differential growth trajectories in infancy and childhood, nor body composition differences at 54 months. **The combination of prenatal multiple micronutrient supplementation (MMS) and BFC was unfavourable for linear growth during 0-54 months, which raises questions about possible negative effects of MMS.**

Am J Clin Nutr. 2014 Mar;99(3):617-23. doi: 10.3945/ajcn.113.076588. Epub 2013 Dec 24.

Lipid-based nutrient supplements do not decrease breast milk intake of Malawian infants.

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BACKGROUND:
The potential for small-quantity lipid-based nutrient supplements (LNS) to promote growth and development after 6 mo of age is currently being investigated. **Because infants self-regulate energy intake, consumption of LNS may reduce breast milk intake and potentially decrease the beneficial effects of breast milk.**

OBJECTIVE: **The objective was to test the hypothesis that the breast milk intake of 9- to 10-mo-old rural Malawian infants receiving LNS would not be lower than that of infants receiving no supplementation.**

DESIGN: This was a substudy of the International Lipid-based Nutrient Supplements (iLiNS) DOSE trial, in which **6-mo-old infants were randomly assigned to receive 10, 20, or 40 g LNS/d containing 56, 117, or 241 kcal/d, respectively, or no LNS until 18 mo of age. A subset was randomly selected to estimate breast milk intake at 9-10 mo of age with the dose-to-mother deuterium oxide dilution method.** The noninferiority margin was <10% of total energy requirements.

RESULTS: Baseline characteristics (n = 376) were similar across groups. The mean (± SD) daily breast milk intake of unsupplemented infants was 730 ± 226 g. The differences (95% CIs) in mean intake of infants provided with 10, 20, or 40 g LNS/d, compared with controls, were +62 (-18, +143), +30 (-40, +99), and +2 (-68, +72) g/d, respectively. Non-breast milk oral water intake did not differ by group (P = 0.39) and was inversely (r = -0.22, P < 0.01) associated with breast milk intake.

CONCLUSION: **In this rural Malawian population, breast milk intake at 9-10 mo of age was not reduced by supplementation with complementary foods with 10-40 g LNS/d.**

Int J Food Sci Nutr. 2013 Sep;64(6):711-4. doi: 10.3109/09637486.2013.775229. Epub 2013 Mar 12.

Effects of synbiotic supplementation on lactating mothers' energy intake and BMI, and infants' growth.

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In this randomized, double-blind, placebo-controlled trial, **80 lactating mothers were randomly divided into two groups to receive daily supplement of synbiotic (n = 40) or a placebo (n = 40) for 30 days.** Information on dietary intake was collected and anthropometric measurements were taken using standard calibrated instruments. Data analysis was carried out using nutritionist IV, SPSS and Epi Info software. **Synbiotic supplementation resulted in a slight increase in mean energy intake while, in the placebo group, maternal energy intake decreased significantly (p < 0.023).** Although maternal weight and BMI increased slightly in the supplemented group, these two parameters decreased significantly in the placebo group

($p < 0.01$). Also, infants' weight gain in the synbiotic group was significantly higher than the placebo group after the intervention ($p < 0.044$). **Synbiotics may prevent weight loss in lactating mothers and result in weight gain in infants. Further experiments are required to study these effects in undernourished lactating mothers and their infants.**

Child Care Health Dev. 2014 Jun 9. doi: 10.1111/cch.12166. [Epub ahead of print]

A randomized controlled trial of burping for the prevention of colic and regurgitation in healthy infants.

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BACKGROUND: Efficacy of burping in lowering colic and regurgitation episodes in healthy term babies lacks evidence in literature.

METHODS: **We conducted a randomized controlled trial to compare efficacy of burping versus no-burping in 71 mother-baby dyads in community setting.** Primary outcome was reduction in event rates of colic and regurgitation episodes over 3 months.

RESULTS: Baseline characteristics were similar in two groups. Difference in incidence rates of colic between the control and burping group was 1.57 episodes/infant/100 weeks [95% confidence interval (CI): -0.63 to 3.76]. **There was statistically no significant reduction in colic episodes between burping and non-burping study subjects during 3 months of follow-up (adjusted relative risk 0.64; 95% CI: 0.22-1.86, P-value 0.41). Incidence rate difference of regurgitation episodes/infant/week between burping and control group was 4.36 (95% CI: 4.04 to 4.69) and there was statistically significant increase in burping group (adjusted relative risk 2.05; 95% CI: 1.92-2.18, P-value < 0.0001).**

CONCLUSIONS: **Although burping is a rite of passage, our study showed that burping did not significantly lower colic events and there was significant increase in regurgitation episodes in healthy term infants up to 3 months of follow-up.**

Macronutrient nutrition and complementary feeding

(See also Vitamin A)

Am J Clin Nutr. 2013 Oct;98(4):983-93. doi: 10.3945/ajcn.112.053595. Epub 2013 Aug 14.

Efficacy and safety of new complementary feeding guidelines with an emphasis on red meat consumption: a randomized trial in Bogota, Colombia.

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BACKGROUND: Iron deficiency and poor linear growth are common in infants from deprived socioeconomic backgrounds and may be associated with inadequate complementary feeding (CF) practices.

OBJECTIVE: **We tested the hypothesis that new CF guidelines emphasizing meat as a source of iron and zinc would improve linear growth, iron, and zinc status in infants living in poor socioeconomic circumstances in Bogota, Colombia.**

DESIGN: **A total of 85 term infants who were exclusively breastfed for ≥4 mo were randomly assigned at 6 mo of age to a control group [CG (n = 43); current advice] or intervention group (new guidelines group [NGG (n = 42); with counseling to 1) continue breastfeeding, 2) offer red meat ≥3 d/wk, and 3) offer fruit and vegetables daily]).** Main outcomes were 1) linear growth from 6 to 12 mo of age; 2) hemoglobin, hematocrit, iron [serum ferritin (SF)], and zinc status at 12 mo of age; and 3) meat intake at 12 mo of age (by using a food-frequency questionnaire).

RESULTS: **A total of 38 infants/group provided data at 12 mo of age. NGG infants had significantly higher red meat intake [mean ± SD: 5.4 ± 1.8 compared with 3.5 ± 1.7 d/wk at 12 mo of age; P < 0.001), higher hemoglobin and hematocrit at 12 mo of age, and a significantly greater increase in hemoglobin (mean ± SD change: 0.41 ± 0.8 compared with -0.13 ± 1.0; P = 0.01) and hematocrit (1.04 ± 2.2 compared with -0.15 ± 2.4; P = 0.03) from 6 to 12 mo of age than those in CG infants.** There were no significant differences in linear growth from 6 to 12 mo of age or in SF or zinc.

CONCLUSIONS: **The new guidelines showed efficacy with higher red meat intake and positive effects on hemoglobin and hematocrit.** The intervention was acceptable and affordable for most mothers. These preliminary results suggest that the intervention merits investigation in a larger cohort with longer-term follow-up. This trial was registered at http://isrctn.org as ISRCTN57733004.

Br J Nutr. 2014 Feb;111(3):499-505. doi: 10.1017/S0007114513002857. Epub 2013 Aug 23.

Diet quality from pre-school to school age in Brazilian children: a 4-year follow-up in a randomised control study.

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A previous study demonstrated that dietary counselling for mothers during the first year of life improved overall diet quality of children at pre-school age in a low-income population. Thus, the objective of the present study was to assess the long-term effect of this intervention on diet quality of children at school age and examine the tracking of dietary intake throughout childhood. The present study was a follow-up of a randomised controlled trial with children who were assessed at 3-4 years (n 345) and 7-8 years (n 307) of age. We collected two 24 h dietary recalls and assessed diet quality using the Healthy Eating Index (HEI). Analyses were

performed by group using a paired t test and a Student's t test for independent samples. Diet quality did not differ between the intervention and control groups at 7-8 years of age (HEI score 65·2 (SD 9·5) v. 64·9 (SD 8·5)). Regarding changes in diet quality from pre-school to school age, we observed the tracking of diet quality in the control group and the loss of the intervention effect in the intervention group. In both groups, the score for fruit and milk intake decreased, while that for saturated fat and dietary variety intake increased. The score for the intakes of grains, meat and legumes, and total fat remained constant for all children. The present data provide evidence that diet quality tracks during childhood since the total HEI score did not differ over time in the control group. The decrease in score for some HEI components did not affect the overall diet quality due to the increase in score for other HEI components.

Oncology

(see also HIV – management of HIV related conditions)

Pediatr Blood Cancer. 2013 Oct;60(10):1593-7. doi: 10.1002/pbc.24570. Epub 2013 Jun 3.

A medication diary-book for pediatric patients with acute lymphoblastic leukemia in Indonesia.

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BACKGROUND: Event-free survival of pediatric patients with acute lymphoblastic leukemia (ALL) in Yogyakarta, Indonesia was low (20%). The aim of the study was to evaluate the effectiveness of using a medication diary-book on the treatment outcome of childhood ALL.

PROCEDURE: A randomized study was conducted with 109 pediatric patients with ALL in a pediatric oncology center in Yogyakarta, Indonesia. Both intervention and control groups received a structured parental education program and donated chemotherapy. **The intervention group received a medication diary-book to remind parents and families to take oral chemotherapy and present for scheduled appointments or admissions.** Event-free survival estimate (EFS) at 3 years was assessed.

RESULTS: **Among pediatric patients with ALL with highly educated mothers (senior high school or higher), the EFS-estimate at 3 years of the intervention group was significantly higher than the EFS-estimate at 3 years of the control group (62% vs. 29%, P = 0.04).** Among pediatric patients with ALL with low-educated mothers, no significant difference was found in the EFS-estimates at 3 years between the intervention and control group (26% vs. 18%, P = 0.86).

CONCLUSIONS: We conclude that a medication diary-book might be useful to improve the survival of pediatric patients with ALL in resource-limited settings, particularly in patients with highly educated mothers.

http://onlinelibrary.wiley.com/store/10.1002/pbc.24570/asset/pbc24570.pdf?v=1&t=hxd3jf95&s=5815715a76fb5d581c6ada221aee9776d30489db

J Clin Oncol. 2014 Jan 20;32(3):174-84. doi: 10.1200/JCO.2013.48.6522. Epub 2013 Dec 16.

Intensive chemotherapy for childhood acute lymphoblastic leukemia: results of the randomized intercontinental trial ALL IC-BFM 2002.

Stary J[1], Zimmermann M, Campbell M, Castillo L, Dibar E, Donska S, Gonzalez A, Izraeli S, Janic D, Jazbec J, Konja J, Kaiserova E, Kowalczyk J, Kovacs G, Li CK, Magyarosy E, Popa A, Stark B, Jabali Y, Trka J, Hrusak O, Riehm H, Masera G, Schrappe M.

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PURPOSE: From 2002 to 2007, the International Berlin-Frankfurt-Münster Study Group conducted a prospective randomized clinical trial (ALL IC-BFM 2002) for the management of childhood acute lymphoblastic leukemia (ALL) in 15 countries on three continents. The aim of this trial was to explore the impact of differential delayed intensification (DI) on outcome in all risk groups.

PATIENTS AND METHODS: For this trial, 5,060 eligible patients were divided into three risk groups according to age, WBC, early treatment response, and unfavorable genetic aberrations. DI was randomized as follows: standard risk (SR), two 4-week intensive elements (protocol III) versus one 7-week protocol II; intermediate risk (IR), protocol III × 3 versus protocol II × 1; high risk (HR), protocol III × 3 versus either protocol II × 2 (Associazione Italiana Ematologia Oncologia Pediatrica [AIEOP] option), or 3 HR blocks plus single protocol II (Berlin-Frankfurt-Münster [BFM] option).

RESULTS: **At 5 years, the probabilities of event-free survival and survival were 74% (± 1%) and 82% (± 1%) for all 5,060 eligible patients, 81% and 90% for the SR (n = 1,564), 75% and 83% for the IR (n = 2,650), and 55% and 62% for the HR (n = 846) groups, respectively. No improvement was accomplished by more intense and/or prolonged DI.**

CONCLUSION: The ALL IC-BFM 2002 trial is a good example of international collaboration in pediatric oncology. A wide platform of countries able to run randomized studies in ALL has been established. Although the alternative DI did not improve outcome compared with standard

treatment and the overall results are worse than those achieved by longer established leukemia groups, the national results have generally improved.

Psychooncology. 2013 Nov;22(11):2601-10. doi: 10.1002/pon.3326. Epub 2013 Jun 4.

Effectiveness of an integrated adventure-based training and health education program in promoting regular physical activity among childhood cancer survivors.

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BACKGROUND: There is growing concern about declining levels of physical activity in childhood cancer survivors. This study aimed to examine the effectiveness of an integrated adventure-based training and health education program in promoting changes in exercise behavior and enhancing the physical activity levels, self-efficacy, and quality of life of Hong Kong Chinese childhood cancer survivors.

METHODS: A randomized controlled trial, two-group pretest and repeated post-test, between-subjects design was conducted to 71 childhood cancer survivors (9- to 16-year-olds). **Participants in the experimental group joined a 4-day integrated adventure-based training and health education program. Control group participants received the same amount of time and attention as the experimental group but not in such a way as to have any specific effect on the outcome measures.** Participants' exercise behavior changes, levels of physical activity, self-efficacy, and quality of life were assessed at the time of recruitment, 3, 6, and 9 months after starting the intervention.

RESULTS: **Participants in the experimental group reported statistically significant differences in physical activity stages of change ($p < 0.001$), higher levels of physical activity ($p < 0.001$) and self-efficacy ($p = 0.04$) than those in the control group.** Besides, there were statistically significant mean differences ($p < 0.001$) in physical activity levels (-2.6), self-efficacy (-2.0), and quality of life (-4.3) of participants in the experimental group from baseline to 9 months after starting the intervention.

Ophthalmology

Am J Ophthalmol. 2013 Jul;156(1):178-183.e1. doi: 10.1016/j.ajo.2013.01.031. Epub 2013 Apr 24.

Role of oral corticosteroids in orbital cellulitis.

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PURPOSE: To evaluate the role of oral corticosteroids as an anti-inflammatory adjunct in the treatment of orbital cellulitis.

DESIGN: Prospective, comparative, single-masked, interventional clinical study.

METHODS: Setting: Tertiary eye care center (All India Institute of Medical Sciences). study population: Patients with acute onset (within 14 days) of orbital cellulitis with or without abscess. intervention: Patients were randomized into 2 groups in the ratio of 1:2. Both groups received initial intravenous antibiotics. In Group 2, oral steroids were added after an initial response to intravenous antibiotics. main outcome measures: Resolution of signs and symptoms, duration of intravenous antibiotics, length of hospital stay, and sequelae of disease (ptosis, proptosis, and movement restriction) were evaluated and compared between the 2 groups.

RESULTS: A total of 21 patients (age range, 11-59 years) with orbital cellulitis were studied. **There were 7 patients in Group 1, who received standard intravenous antibiotics, and 14 in Group 2, who received adjuvant steroids. Patients in Group 2 showed an earlier resolution of inflammation in terms of periorbital edema (P = .002 at day 7), conjunctival chemosis (P < .001 at day 10), and pain (P = .012 at day 7).** They also attained vision of 0.02 on logMAR earlier than Group 1 patients. Decrease in proptosis and improvement in extraocular movements were also significantly better with the use of steroids (P = .027 at day 10, P = .003 at day 14, respectively). While a significant number of patients in Group 1 had mild residual ptosis, proptosis, and movement restriction at 12 weeks, none of the patients treated with steroids had any residual changes (P = .023, P = .001, and P = .001, respectively). The durations of intravenous antibiotics and hospital stay were significantly less in Group 2.

CONCLUSION: **Use of oral steroids as an adjunct to intravenous antibiotic therapy for orbital cellulitis may hasten resolution of inflammation with a low risk of exacerbating infection.**

Graefes Arch Clin Exp Ophthalmol. 2014 Mar;252(3):441-7. doi: 10.1007/s00417-014-2571-0. Epub 2014 Jan 19.

Bilateral implantation of multifocal versus monofocal intraocular lens in children above 5 years of age.

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PURPOSE: To evaluate visual results and complications after bilateral implantation of multifocal versus monofocal intraocular lens (IOL) in children above five years of age.

METHODS: In this prospective non-randomized controlled trial, children with bilateral developmental cataract above five years of age were divided into two groups - Group A implanted with multifocal IOL (both refractive and diffractive) and Group B implanted with monofocal IOL in both eyes. Outcome measures of best corrected visual acuity (BCVA) for distance, distance-corrected near visual acuity (DCNVA), mean refractive spherical equivalent (MRSE), contrast sensitivity, stereopsis and complications such as posterior capsular

opacification (PCO) and glare were analyzed using the Mann-Whitney U and the Wilcoxon Signed Rank tests.

RESULTS: Forty-two eyes of 21 children (mean age: 7.19 years, range: 5-12 years) were included in the study. Group A included 14 eyes (seven children) Group B included 28 eyes (14 children). Both groups showed significant improvement in BCVA at one year follow-up, but no significant difference was found on comparing contrast sensitivity. Stereopsis was slightly better in Group A (125.71 arc-sec) as compared to Group B (140 arc-sec) ($p = 0.280$). Most patients in Group A were spectacle-independent for near (71.4 %) versus Group B. MRSE at one year was 0.21 in Group A and 0.5 in Group B. Incidence of PCO was similar in either groups (35.7 %). No intraoperative complication was noted in any child.

CONCLUSION: Multifocal IOL implantation is a viable option in children above five years of age with bilateral cataract.

Br J Ophthalmol. 2014 Jan;98(1):40-5. doi: 10.1136/bjophthalmol-2013-303914. Epub 2013 Oct 29.

Defocus Incorporated Soft Contact (DISC) lens slows myopia progression in Hong Kong Chinese schoolchildren: a 2-year randomised clinical trial.

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AIMS: To determine if 'Defocus Incorporated Soft Contact' (DISC) lens wear slows childhood myopia progression.

METHODS: **A 2-year double-blind randomised controlled trial was carried out in 221 children aged 8-13 years, with myopia between -1.00 and -5.00 Dioptres (D) and astigmatism ≤1.00 D. Subjects were randomly assigned to the DISC (n=111) or single vision (SV; n=110) contact lens group. DISC lenses incorporated concentric rings, which provided an addition of +2.50 D, alternating with the normal distance correction.** Refractive error (cycloplegic autorefraction) and axial length were measured at 6-month intervals. Differences between groups were analysed using unpaired t test.

RESULTS: **In total, 128 children completed the study, n=65 in the DISC group and n=63 in the SV group. Myopia progressed 25% more slowly for children in the DISC group compared with those in the control group** (0.30 D/year; 95% CI -0.71 to -0.47 vs 0.4 D/year; 95% CI -0.93 to -0.65, p=0.031). Likewise, there was less axial elongation for children in the DISC versus SV groups (0.13 mm/year; 95% CI 0.20 to 0.31 vs 0.18 mm/year; 95% CI 0.30 to 0.43, p=0.009). Treatment effect correlated positively with DISC lens wearing time (r=0.342; p=0.005). Indeed, myopia in children who wore the DISC lenses for five or more hours/day progressed 46% (mean difference=-0.382 D, p=0.001; 95% CI -0.59 to -0.17) less than those in the SV group.

CONCLUSIONS: **The daily wearing of DISC lens significantly slowed myopia progression and axial elongation in Hong Kong schoolchildren.** The findings demonstrated that simultaneous clear vision with constant myopic defocus can retard myopia progression.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24169657/

Anaesthesia. 2013 Jul;68(7):747-52. doi: 10.1111/anae.12286.

A randomised comparison of lidocaine 2% gel and proparacaine 0.5% eye drops in paediatric squint surgery.

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We conducted **a randomised trial comparing lidocaine 2% gel with proparacaine 0.5% eye drops in children having elective squint surgery.** One hundred and forty children aged between 3 and 14 years were recruited. The requirement for intra-operative fentanyl and postoperative ibuprofen was significantly less in the lidocaine group compared with the proparacaine group (1 (1.7%) vs 12 (18.5%), p=0.002 and 16 (27.6%) 38 (58.5%), p=0.001, respectively). **The incidence of postoperative nausea and vomiting was significantly less in the lidocaine group compared with the proparacaine group (6 (10.3%) vs 16 (24.6%), p=0.04).** There were no differences between the groups in terms of incidence and severity of the oculocardiac reflex. We conclude that, compared with proparacaine 0.5% eye drops, a single application of lidocaine 2% gel improves peri-operative analgesia and reduces the incidence of postoperative nausea and vomiting in elective paediatric squint surgery.

http://onlinelibrary.wiley.com/store/10.1111/anae.12286/asset/anae12286.pdf?v=1&t=hxd3ltjt&s=84205b25acc63407b02ac46a6c2789261f723eaa

Trachoma

(See also Hygiene)

Invest Ophthalmol Vis Sci. 2014 Apr 11;55(4):2307-14. doi: 10.1167/iovs.13-12701.

Cohort and age effects of mass drug administration on prevalence of trachoma: a longitudinal study in rural Tanzania.

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PURPOSE: Mass drug administration (MDA) is part of the SAFE strategy for trachoma elimination. This study examined the effect of three annual MDAs on prevalence of trachoma among 13 longitudinal cohorts of Tanzanian children.

METHODS: Children younger than 10 years were assigned to cohorts based on age at baseline and followed annually for 3 years, with newborns assigned to new cohorts over time. **Annual MDA consisted of topical tetracycline for children younger than 6 months and oral azithromycin for those 6 months and older.** Follicular trachoma (TF) and Chlamydia

trachomatis infection status were assessed annually before the next MDA. Prevalence and risk factors for TF and infection at each age were compared across cohorts.

RESULTS: **At each survey, most age groups and cohorts had MDA coverage of more than 80% and showed decreased TF prevalence after every MDA.** One cohort had consistently lower coverage, higher-than-expected TF and infection at ages 6 and 7, and elevated risk of TF at age 7 relative to the preceding cohort in spite of receiving one additional MDA (odds ratio 2.3, 95% confidence interval 1.0-5.2). Cohorts aged 1 or older at baseline generally showed reductions in TF and infection after each MDA, whereas younger cohorts showed decreased infection but increased TF over time. Successive cohorts of never-treated children younger than 1 year showed sequential TF and infection reductions with each MDA ($P < 0.001$).

CONCLUSIONS: **Multiple MDAs significantly reduce trachoma prevalence and appear to increasingly protect children born into these communities.** The youngest children show declining/stable rates of infection but increasing rates of trachoma, which may reflect longer duration of clinical signs.

Am J Trop Med Hyg. 2013 Oct;89(4):717-20. doi: 10.4269/ajtmh.13-0299. Epub 2013 Sep 3.

The association between latrine use and trachoma: a secondary cohort analysis from a randomized clinical trial.

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Latrine use has been promoted as a component of an integrated strategy for trachoma control. As part of a randomized trial in Ethiopia, **12 communities received a mass azithromycin distribution followed by a latrine promotion intervention.** A random sample of children ages 0-9 years in each community was monitored longitudinally for ocular chlamydia. After latrine construction ended, those **communities with a higher proportion of households using latrines were more likely to experience a reduction in the prevalence of ocular chlamydia.** Specifically, for each 10% increase in latrine use, there was a 2.0% decrease (95% confidence interval = 0.2-3.9% decrease) in the community prevalence of ocular chlamydia over the subsequent year ($P = 0.04$).

PLoS Negl Trop Dis. 2013 Jul 25;7(7):e2347. doi: 10.1371/journal.pntd.0002347. Print 2013.

Association between ocular bacterial carriage and follicular trachoma following mass azithromycin distribution in The Gambia.

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BACKGROUND: Trachoma, caused by ocular Chlamydia trachomatis infection, is the leading infectious cause of blindness, but its prevalence is now falling in many countries. **As the prevalence falls, an increasing proportion of individuals with clinical signs of follicular trachoma (TF) is not infected with C. trachomatis. A recent study in Tanzania suggested that other bacteria may play a role in the persistence of these clinical signs.**

METHODOLOGY/PRINCIPAL FINDINGS: We examined associations between clinical signs of TF and ocular colonization with four pathogens commonly found in the nasopharnyx, three years after the initiation of mass azithromycin distribution. Children aged 0 to 5 years were randomly selected from 16 Gambian communities. Both eyes of each child were examined and graded for trachoma according to the World Health Organization (WHO) simplified system. Two swabs were taken from the right eye: one swab was processed for polymerase chain reaction (PCR) using the Amplicor test for detection of C. trachomatis DNA and the second swab was processed by routine bacteriology to assay for the presence of viable Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus and Moraxella catarrhalis. Prevalence of TF was 6.2% (96/1538) while prevalence of ocular C. trachomatis infection was 1.0% (16/1538). **After adjustment, increased odds of TF were observed in the presence of C. trachomatis (OR = 10.4, 95%CI 1.32-81.2, p = 0.03), S. pneumoniae (OR = 2.14, 95%CI 1.03-4.44, p = 0.04) and H. influenzae (OR = 4.72, 95% CI 1.53-14.5, p = 0.01).**

CONCLUSIONS/SIGNIFICANCE: **Clinical signs of TF can persist in communities even when ocular C. trachomatis infection has been controlled through mass azithromycin distribution. In these settings, TF may be associated with ocular colonization with bacteria commonly carried in the nasopharnyx.** This may affect the interpretation of impact surveys and the determinations of thresholds for discontinuing mass drug administration.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23936573/

Oral health / dentistry

(See Health education)

J Int Oral Health. 2013 Oct;5(5):33-7. Epub 2013 Oct 26.

Evaluation of the efficacy of probiotics in plaque reduction and gingival health maintenance among school children - A Randomized Control Trial.

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BACKGROUND: Probiotics are live micro-organisms that when administered in adequate amounts confer health benefits upon the host. The impact of probiotics on oral health is relatively new with lots of research going on; the area of probiotics and periodontal disease is

still in its infancy. The aim of the present trial was to evaluate the efficacy of the probiotics in plaque reduction among school children.

MATERIALS & METHODS:**This is a randomized, double-blind, placebo controlled parallel design study involving 216 school children (aged 14 - 17 years): 108 as experimental subjects and 108 as controls.** Complete oral prophylaxes were performed for both the control group and experimental group. The pre-intervention plaque index and gingival index were recorded one week after the prophylaxis for both groups as the baseline data. **The study subjects (Group A) included curd in their daily diet for 30 days, while the control subjects (Group B) excluded curd in their diet for 30 days.** The post intervention plaque index and gingival index were recorded again and statistically compared with the baseline data. **Results: the intervention group (Group A) was found to have statistically significant reduction in plaque when compared to that of the control group with p <0.001 and there was no significant improvement in gingival health.**

CONCLUSION: **A short-term daily ingestion of probiotics delivered via curd in diet reduced the levels of plaque.** Hence if it can be promoted in the regular diet, it would help in improving the oral health among school children.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24324302/

J Dent Res. 2013 Jul;92(7 Suppl):29S-36S. doi: 10.1177/0022034513484331. Epub 2013 May 20.

Cluster-randomized trial of infant nutrition training for caries prevention.

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The objective of this study was to estimate the caries impact of providing training in infant feeding guidelines to workers at Brazilian public primary care clinics. **In a cluster-randomized controlled trial (n = 20 clinics), health care workers either were trained in guidelines for infant nutrition, stressing healthful complementary feeding, or were assigned to a 'usual practices' control, which allowed for maternal counseling at practitioner discretion**. Training occurred once; the amount of counseling provided to mothers was not assessed. Eligible pregnant women were enrolled to follow health outcomes in their children. Early childhood caries (ECC) was measured at age three years (n = 458 children). **The overall reductions in ECC (relative risk, 0.92; 95%CI, 0.75, 1.12) and severe ECC (RR, 0.87; 95%CI, 0.64, 1.19) were not statistically significant.** There was a protective effect among mothers who remained exclusively at the same health center (S-ECC RR, 0.68; 95%CI, 0.47, 0.99) and among those naming the health center as their principal source of feeding advice (S-ECC RR, 0.53; 95%CI, 0.29, 0.97). Health care worker training did not yield a statistically significant reduction in caries overall, although caries was reduced among children of mothers more connected to their health centers.

J Indian Soc Pedod Prev Dent. 2014 Jan-Mar;32(1):48-52. doi: 10.4103/0970-4388.127055.

Comparison of behavioral response to caries removal methods: a randomised controlled cross over trial.

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BACKGROUND: The issue of dental fear and anxiety still poses a significant problem in treating children. Various caries management protocols have been tried to make the dental visit more compatible to the child patients.

AIM: The aim of the study was to evaluate and compare the behavioral and physiological responses to chemo-mechanical caries removal (CMCR) and conventional drilling method (CDM).

MATERIALS AND METHODS: **A total of 20 children with an age range of 7 to 11 years with bilateral frank carious lesions were included in this study. They were randomized into two groups: Group A--treated with CDM first followed by CMCR and Group B--treated with CMCR first followed by CDM.** The physiological signs (pulse, blood pressure and oxygen saturation) were noted prior to treatment, during treatment, post treatment and 5 min after treatment. The behavioral responses were assessed by face, legs, activity, cry, and consolability scale and facial image scale. The participants were interviewed about pain, discomfort, taste, smell, preference and overall experience after every procedure. The pediatric dentist filled in details about patient behavior, time utilized and need for local anesthesia. The results were statistically analyzed using t-test and Chi-square test appropriately (SPSS version 11).

RESULTS: **There was no significant difference in any of the physiological parameters assessed between the two groups. Discomfort was significantly more ($P < 0.025$) in the CDM group than CMCR group. The time taken by the dentist was significantly lesser ($P < 0.01$) in the CDM group.**

CONCLUSION: Techniques which enhance the behavioral response in children should be considered for a better pediatric dental practice.

J Investig Clin Dent. 2014 May 22. doi: 10.1111/jicd.12094. [Epub ahead of print]

Efficacy of triphala mouth rinse (aqueous extracts) on dental plaque and gingivitis in children.

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AIM: The aim of the present study was to evaluate the efficacy of triphala mouth rinse (aqueous) in the reduction of plaque and gingivitis among children.

METHODS: **The study was a randomized, double-blinded, controlled trial, with a total of 60 school children (n = 30 in each group; triphala and chlorhexidine groups). Plaque and gingival indices were used to evaluate baseline and follow-up plaque and gingivitis.**

RESULTS: **A total of 57 children completed the study. Both chlorhexidine and triphala groups showed significantly lower mean gingival and plaque index scores at follow up than baseline (P < 0.001). There was no significant difference in the percentage change in the mean gingival index between the two groups (P = 0.826). The percentage change in the mean plaque index was significantly higher in the chlorhexidine group compared to the triphala group (P = 0.048).**

CONCLUSION: The effectiveness of triphala in the reduction of plaque and gingivitis was comparable to chlorhexidine, and can be used for short-term purposes without potential side-effects. It is a cost-effective alternative in reducing plaque and gingivitis.

J Endod. 2014 May;40(5):599-605. doi: 10.1016/j.joen.2014.01.009. Epub 2014 Mar 6.

Comparative evaluation of platelet-rich fibrin and mineral trioxide aggregate as pulpotomy agents in permanent teeth with incomplete root development: a randomized controlled trial.

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INTRODUCTION: The purpose of this study was to evaluate and compare, clinically and radiographically, the effects of platelet-rich fibrin (PRF) and mineral trioxide aggregate (MTA) as pulpotomy agents in permanent teeth with incomplete root development.

METHODS: A total number of 70 children requiring pulpotomy in 70 permanent molars with incomplete root development were screened. Sixty-two patients met the inclusion criteria and were enrolled in the study. The patients were randomly allocated equally in 2 treatment groups. **MTA pulpotomy was performed in group A (the control group), and PRF pulpotomy was performed in group B (the experimental group).** The treated teeth were restored with amalgam followed by stainless steel crowns. Clinical and radiographic evaluations were performed after 6, 12, and 24 months. Thus, the data obtained were blindly analyzed using the chi-square test.

RESULTS: **There was no significant difference between the 2 groups in terms of clinical and radiologic success.** Radiographically, all available cases (53 teeth) showed evidence of root growth and canal narrowing. Complete apical closure was observed in 88.8% in the PRF group (experimental group) and 80.07% of roots in the MTA group (control group), respectively, at 24 months.

CONCLUSIONS: PRF could be used as a suitable biological and economic alternative to MTA in pulpotomy procedures of permanent teeth with incomplete root development.

Int Dent J. 2013 Dec;63(6):329-35.

Effect of different protocols for treating cavities in primary molars on the quality of life of children in Brazil--1 year follow-up.

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The aim of this study was to test the hypothesis that the conventional restorative treatment (CRT) and the atraumatic restorative treatment (ART) protocols, in comparison with the ultra-conservative treatment (UCT) protocol, would increase the quality of life of children over a period of 1 year. **Cavitated primary molars of 302 children 6-7 years of age were treated according to the CRT, ART and UCT protocols at the school compound.** Children's parents completed the **Brazilian version of the Early Childhood Oral Health Impact Scale (B-ECOHIS) at baseline and one year later.** Paired t-test, Chi-square test and ANOVA were applied in analysing the data. Questionnaires from 277 and 160 children were collected at baseline and after 1 year, respectively. **A statistically significant difference in B-ECOHIS scores over the 1-year period was found for domains 'child symptoms' (P = 0.03) and 'child psychology' (P = 0.02).** Treatment protocols did not statistically significantly influence the changes in B-ECOHIS scores over the 1-year period (P = 0.78). It can be concluded that the UCT protocol was as good as the two restorative protocols. All treatment protocols were effective in reducing children's experience of pain, their sleeping problems and their irritability and/or frustration levels over the 1-year period.

J Clin Pediatr Dent. 2013 Fall;38(1):67-70.

A randomized trial on the inhibitory effect of chewing gum containing tea polyphenol on caries.

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OBJECTIVE: **The purpose of the study was to determine the cariostatic potential of a chewing gum containing tea polyphenol**.

STUDY DESIGN: A total of 157 schoolchildren aged 8-9 years were randomly allocated into three groups. Two groups received chewing gum with or without tea polyphenol. A third group did not receive any chewing gum. A single examiner assessed the caries status for all participates at baseline, 12 months and 24 months. A one-way analysis of variance (ANOVA) was performed to evaluate differences among the groups at each interval The Chi-square test was used to compare the caries-free rate among the three groups.

RESULTS: The mean DMFT increment was 0.17 for the polyphenol gum group, 0.60 for the control gum group, and 1.15 for the no gum group. **Children who chewed gum containing tea**

polyphenol had a significantly lower mean DMFS increment over the 24-month period than did the other two groups ($p < 0.05$). The caries-free rate in the polyphenol gum group was significantly higher than that in the other two groups ($p < 0.05$) after two years.

CONCLUSION: **These findings indicated that the oral application of chewing gum with tea polyphenol has an inhibitory effect on dental caries.**

Eur J Paediatr Dent. 2013 Dec;14(4):273-8.

Efficacy trial of Camouflage Syringe to reduce dental fear and anxiety.

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AIM: Dental fear and anxiety in early childhood are widely prevalent and contribute to dental problems and behaviour in adulthood. Novel ways to reduce dental fear and anxiety in children are needed. Our aim was to conduct an efficacy trial of a novel Camouflage Syringe to reduce dental fear and anxiety in children.

MATERIALS AND METHODS: Study Design: randomised controlled trial of efficacy of the Camouflage Syringe. We designed a Camouflage Syringe with a toy-like appearance that veils the conventional syringe to permit topical application and injection of local anaesthesia and ensure more involvement of the patient in the treatment process. We conducted a concurrent parallel, randomised controlled trial (NCT01398007) on the efficacy of this Camouflage Syringe to reduce the dental fear and anxiety in children seeking dental treatment who required the use of local anaesthesia.

RESULTS: Using Venham's clinical rating scale, Venham's picture test, parental stress questionnaire and recall questionnaire, the efficacy of the Camouflage Syringe to reduce dental fear and anxiety ranged from 82% to 97% for various outcomes and from 60% to 100% for prevention of related adverse outcomes. For all outcomes, the number needed to treat was close to unity.

CONCLUSION: Our results strongly favour the use of Camouflage Syringe to reduce dental fear and anxiety in children.

Int J Dent Hyg. 2013 Aug;11(3):191-7. doi: 10.1111/idh.12028. Epub 2013 May 30.

Comparative evaluation of chlorhexidine varnish and fluoride varnish on plaque Streptococcus mutans count--an in vivo study.

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AIM: **The aim of the study was to assess and compare the effect of chlorhexidine varnish and fluoride varnish application on Streptococcus mutans counts in plaque of occlusal pits and fissures of permanent mandibular first molars.**

MATERIALS AND METHODS: The study was an in vivo comparative study, conducted among 50 schoolchildren aged 7-8 years under a field setting. The 50 subjects were randomly allocated into two groups. Baseline plaque samples were collected from all the subjects followed by the application of two varnishes, Cervitec and Duraphat. The varnish was applied to pit and fissures of occlusal surface of mandibular first molar. The varnish application was carried out on the first day, fifth day and tenth day after baseline plaque sampling. Subsequent plaque samples were collected at the end of 1 month and at the end of 3 months after the varnish application.

RESULTS: The Cervitec varnish has shown a statistically significant reduction at the end of 1 month and at the end of 3 months ($P < 0.05$). Duraphat varnish did not show a statistically significant difference in reducing the plaque S. mutans count at the end of 1 month and third month ($P > 0.05$).

CONCLUSION: Cervitec varnish was found to be effective in reducing S. mutans count for a 3-month period, when compared to Duraphat varnish.

J Clin Pediatr Dent. 2013 Fall;38(1):45-7.

A novel distraction technique for pain management during local anesthesia administration in pediatric patients.

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AIM: The aim of this study was to assess the effect of an active and novel distraction technique WITAUL (Writing In The Air Using Leg) on the pain behavior observed and reported by children receiving local anesthesia injections prior to dental treatment.

STUDY DESIGN: The study was conducted on 160 children (80 in control and 80 in intervention group) between the ages of 4- 10 years. During the administration of anesthesia the children in the control group were made to relax by means of deep breathing and those in the intervention group were taught to use the WITAUL distraction technique. the behavior of the children aged 4- 5 years was noted using the Modified Toddler- Preschooler Post operative Pain Scale (TPPPS) and that of children aged above 6 years was measured using the FACES Pain Scale-Revised (FPS-R).

RESULTS: The use of WITAUL was found to be statistically significant (p value < 0.0001) compared to the control method in serving as a distraction and hence in managing pain during local anesthesia administration. The mean Modified TPPPS scores (4- 5 year olds) for the WITAL group was 2.46 +/- 1.752 and that of the control was 5.64 +/- 2.328. The mean FPS-R scores (6 - 10 year olds) for the WITAUL group was 3 +/- 1.748 and that of the control group was 6.26 +/- 1.858.

CONCLUSION: The WITAUL technique therefore appears to be a simple and effective method of distraction during local anesthesia administration in pediatric patients.

J Clin Pediatr Dent. 2013 Summer;37(4):415-20.

A double blind randomized trial of ketofol versus propofol for endodontic treatment of anxious pediatric patients.

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OBJECTIVE: To find out the safe and efficient sedative agent for primary molar pulpectomy in uncooperative pediatric patients.

STUDY DESIGN: This double blind randomized trial enrolled 40 anxious and healthy 2-6 year olds. **All subjects received IV propofol (1-1.5 mg/kg) or ketofol (1-1.5 mg/kg propofol with 0.25 mg/kg ketamine) as per group assignment after oral midazolam premedication (0.5 mg/kg).** Sedation maintenance was done with propofol infusion at 25-75 microg/kg/min titrated to a predefined Worse level as per Houpt's sedation rating scale. Additional bolus/es was/were administered in the dosage similar to induction dose in case of inadequate sedation. Primary outcomes were intraoperative and postoperative adverse events. Secondary outcomes were vital signs, success of procedure, operator satisfaction, sedation quality, treatment time, recovery time and total propofol dose.

RESULTS: **Significantly greater incidence of respiratory depression was reported for ketofol group (11/20; 55%) when compared to propofol group (3/20; 15%) (p = 0.008). Desaturation was the most common adverse respiratory event with significantly greater incidence in ketofol group (9/20; 45%) when compared to propofol only group (3/20; 15%) (p = 0.033).** No significant differences regarding secondary outcomes were reported in two groups.

CONCLUSION: Both the regimen exhibited similar sedation profile while propofol alone emerged as a safer option.

Research methods

J Acquir Immune Defic Syndr. 2014 Feb 1;65(2):e86-8. doi: 10.1097/QAI.0b013e3182a9c72b.

Opinions and attitudes of participants in a randomized controlled trial examining the efficacy of SMS reminders to enhance antiretroviral adherence: a cross-sectional survey.

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Schistosomiasis

Bull Soc Pathol Exot. 2013 Aug;106(3):167-9. doi: 10.1007/s13149-013-0289-6. Epub 2013 May 17.

Comparison of the efficacy and safety of praziquantel administered in single dose of 40 versus 60 mg/kg for treating urinary schistosomiasis in Mauritania

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During the last twenty years, praziquantel (PZQ) was the drug of choice for the treatment of schistosomiasis in the majority of national programs. However, a lower rate of cure had been significantly noted on the left bank of the Senegal River. To explain this unusual rate of cure, the assumption of a possible resistance to the drug as well as under-dosing was considered. With an aim of testing this hypothesis of underdosing, **we compared the amount of a single dose of 60 mg/kg of PZQ versus the standardized dose of 40 mg/kg used in curing urinary schistosomiasis in Mauritania. One hundred and fifty-one children aged from 10 to 19 years, including 77 in the group of 60 mg/kg and 74 in the group of 40 mg/ kg, were included in the study. The rates of cure were respectively 64.8% for 60 mg/kg and 67.5% for 40 mg/kg three weeks after the administration of the treatment without statistically significant difference.** For the majority of the patients, the drug was well tolerated and no serious adverse events were noted; however, clinical signs in the form of abdominal pain associated or not with diarrhea and vomiting were noted. Praziquantel remains an effective and well-tolerated drug: the amount of 40 mg/kg of body weight can still be maintained for the treatment of schistosomiasis in Mauritania.

School health and education

(See Nutrition, Ophthalmology, Adolescent health, Anaemia and iron deficiency)

Am J Trop Med Hyg. 2013 Nov;89(5):875-83. doi: 10.4269/ajtmh.13-0237. Epub 2013 Sep 9.

The impact of a school-based hygiene, water quality and sanitation intervention on soil-transmitted helminth reinfection: a cluster-randomized trial.

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We conducted a cluster-randomized trial to assess the impact of a school-based water treatment, hygiene, and sanitation program on reducing infection with soil-transmitted helminths (STHs) after school-based deworming. We assessed infection with STHs at baseline and then at two follow-up rounds 8 and 10 months after deworming. Forty government primary schools in Nyanza Province, Kenya were randomly selected and assigned to intervention or control arms. **The intervention reduced reinfection prevalence (odds ratio [OR] 0.56, 95% confidence interval [CI] 0.31-1.00) and egg count (rate ratio [RR] 0.34, CI 0.15-0.75) of Ascaris lumbricoides. We found no evidence of significant intervention effects on the overall prevalence and intensity of Trichuris trichiura, hookworm, or Schistosoma mansoni reinfection.** Provision of school-based sanitation, water quality, and hygiene improvements may reduce reinfection of STHs after school-based deworming, but the magnitude of the effects may be sex- and helminth species-specific.

Epidemiol Infect. 2014 Feb;142(2):340-51. doi: 10.1017/S0950268813001118. Epub 2013 May 24.

The impact of a school-based water supply and treatment, hygiene, and sanitation programme on pupil diarrhoea: a cluster-randomized trial.

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The impact of improved water, sanitation, and hygiene (WASH) access on mitigating illness is well documented, although **impact of school-based WASH on school-aged children has not been rigorously explored.** We conducted a cluster-randomized trial in Nyanza Province, Kenya to assess the impact of a school-based WASH intervention on diarrhoeal disease in primary-school pupils. Two study populations were used: schools with a nearby dry season water source and those without. Pupils attending 'water-available' schools that received hygiene promotion and water treatment (HP&WT) and sanitation improvements showed no difference in period prevalence or duration of illness compared to pupils attending control schools. Those pupils in schools that received only the HP&WT showed similar results. Pupils in 'water-scarce' schools that received a water-supply improvement, HP&WT and sanitation showed a reduction in diarrhoea incidence and days of illness. **Our study revealed mixed results on the impact of improvements to school WASH improvements on pupil diarrhoea.**

Am J Public Health. 2014 Jan;104(1):e91-7. doi: 10.2105/AJPH.2013.301412. Epub 2013 Nov 14.

The impact of school water, sanitation, and hygiene interventions on the health of younger siblings of pupils: a cluster-randomized trial in Kenya.

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OBJECTIVES: We examined the impact of school water, sanitation, and hygiene (WASH) interventions on diarrhea-related outcomes among younger siblings of school-going children.
METHODS: We conducted a cluster-randomized trial among 185 schools in Kenya from 2007 to 2009. We assigned schools to 1 of 2 study groups according to water availability. Multilevel logistic regression models, adjusted for baseline measures, assessed differences between intervention and control arms in 1-week period prevalence of diarrhea and 2-week period prevalence of clinic visits among children younger than 5 years with at least 1 sibling attending a program school.

RESULTS: **Among water-scarce schools, comprehensive WASH improvements were associated with decreased odds of diarrhea (odds ratio [OR] = 0.44; 95% confidence interval [CI] = 0.27, 0.73) and visiting a clinic (OR = 0.36; 95% CI = 0.19, 0.68), relative to control schools.** In our separate study group of schools with greater water availability, school hygiene promotion and water treatment interventions and school sanitation improvements were not associated with differences in diarrhea prevalence between intervention and control schools.

CONCLUSIONS: **In water-scarce areas, school WASH interventions that include robust water supply improvements can reduce diarrheal diseases among young children.**

Am J Trop Med Hyg. 2013 Oct;89(4):698-708. doi: 10.4269/ajtmh.12-0387. Epub 2013 Aug 12.

Impact of regular soap provision to primary schools on hand washing and E. coli hand contamination among pupils in Nyanza Province, Kenya: a cluster-randomized trial.

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We assessed whether supplying soap to primary schools on a regular basis increased pupil hand washing and decreased Escherichia coli hand contamination. Multiple rounds of structured observations of hand washing events after latrine use were conducted in 60 Kenyan schools, and hand rinse samples were collected one time in a subset of schools. The proportion of pupils observed practicing **hand washing with soap (HWWS) events was significantly higher in schools that received a soap provision intervention (32%) and schools that received soap and latrine cleaning materials (38%) compared with controls (3%).** Girls and boys had similar hand washing rates. **There were non-significant reductions in E. coli contamination among intervention school pupils compared with controls.** Removing the barrier of soap procurement can significantly increase availability of soap and hand washing among pupils; however, we discuss limitations in the enabling policy and institutional environment that may have prevented reaching desired levels of HWWS.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23939707/

Am J Trop Med Hyg. 2013 Sep;89(3):411-8. doi: 10.4269/ajtmh.13-0008. Epub 2013 Jul 8.

Access to waterless hand sanitizer improves student hand hygiene behavior in primary schools in Nairobi, Kenya.

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Handwashing is difficult in settings with limited resources and water access. In primary schools within urban Kibera, Kenya, we investigated the impact of providing waterless hand sanitizer on student hand hygiene behavior. **Two schools received a waterless hand sanitizer intervention, two schools received a handwashing with soap intervention, and two schools received no intervention. Hand cleaning behavior after toilet use was monitored for 2 months using structured observation. Hand cleaning after toileting was 82% at sanitizer schools (N = 2,507 toileting events), 38% at soap schools (N = 3,429), and 37% at control schools (N = 2,797).** Students at sanitizer schools were 23% less likely to have observed rhinorrhea than control students (P = 0.02); reductions in student-reported gastrointestinal and respiratory illness symptoms were not statistically significant. Providing waterless hand sanitizer markedly increased student hand cleaning after toilet use, whereas the soap intervention did not. Waterless hand sanitizer may be a promising option to improve student hand cleansing behavior, particularly in schools with limited water access.

Public Health Nutr. 2013 Sep;16(9):1593-604. doi: 10.1017/S1368980013000876. Epub 2013 Mar 28.

School snacks decrease morbidity in Kenyan schoolchildren: a cluster randomized, controlled feeding intervention trial.

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OBJECTIVE: To examine the effects of three different school snacks on morbidity outcomes.

DESIGN: **Twelve schools were randomized to either one of three feeding groups or a Control group.** There were three schools per group in this cluster randomized trial. **Children in feeding group schools received school snacks of a local plant-based dish, githeri, with meat, milk or extra oil added.** The oil used was later found to be fortified with retinol. Physical status, food intake and morbidity outcomes were assessed longitudinally over two years.

SETTING: Rural Embu District, Kenya, an area with high prevalence of vitamin A deficiency.

SUBJECTS: Standard 1 schoolchildren (n 902; analytic sample) enrolled in two cohorts from the same schools one year apart.

RESULTS: **The Meat and Plain Githeri (i.e. githeri+oil) groups showed the greatest declines in the probability of a morbidity outcome (PMO) for total and severe illnesses, malaria, poor appetite, reduced activity, fever and chills. The Meat group showed significantly greater declines in PMO for gastroenteritis (mainly diarrhoea) and typhoid compared with the Control group, for jaundice compared with the Plain Githeri group, and for skin infection compared with the Milk group.** The Milk group showed the greatest decline in PMO for upper respiratory infection. For nearly all morbidity outcomes the Control group had the highest PMO and the least decline over time.

CONCLUSIONS: **The intervention study showed beneficial effects of both animal source foods and of vitamin A-fortified oil on morbidity status.**

Br J Nutr. 2014 Mar 14;111(5):875-86. doi: 10.1017/S0007114513003310. Epub 2013 Oct 30.

Animal source foods have a positive impact on the primary school test scores of Kenyan schoolchildren in a cluster-randomised, controlled feeding intervention trial.

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Micronutrient deficiencies and suboptimal energy intake are widespread in rural Kenya, with detrimental effects on child growth and development. Sporadic school feeding programmes rarely include animal source foods (ASF). **In the present study, a cluster-randomised feeding trial was undertaken to determine the impact of snacks containing ASF on district-wide, end-term standardised school test scores and nutrient intake.** A total of twelve primary schools were randomly assigned to one of three isoenergetic feeding groups (a local plant-based

stew (githeri) with meat, githeri plus whole milk or githeri with added oil) or a control group receiving no intervention feeding. After the initial term that served as baseline, children were fed at school for five consecutive terms over two school years from 1999 to 2001. Longitudinal analysis was used controlling for average energy intake, school attendance, and baseline socio-economic status, age, sex and maternal literacy. Children in the Meat group showed significantly greater improvements in test scores than those in all the other groups, and the Milk group showed significantly greater improvements in test scores than the Plain Githeri (githeri+oil) and Control groups. **Compared with the Control group, the Meat group showed significant improvements in test scores in Arithmetic, English, Kiembu, Kiswahili and Geography. The Milk group showed significant improvements compared with the Control group in test scores in English, Kiswahili, Geography and Science. Folate, Fe, available Fe, energy per body weight, vitamin B_{12}, Zn and riboflavin intake were significant contributors to the change in test scores.** The greater improvements in test scores of children receiving ASF indicate improved academic performance, which can result in greater academic achievement.

Asia Pac J Clin Nutr. 2014;23(1):48-54. doi: 10.6133/apjcn.2014.23.1.04.

A school-based comprehensive lifestyle intervention among Chinese kids against Obesity (CLICK-Obesity) in Nanjing City, China: the baseline data.

Xu F[1], Wang X, Ware RS, Tse LA, Wang Z, Hong X, Chan EY, Li J, Wang Y.

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BACKGROUND: Urgent development of effective interventions to prevent rapidly rising childhood obesity in China is needed.

METHODS: Between May 2010 and December 2013, a cluster randomized controlled trial was conducted among 4th graders in eight urban primary schools randomly assigned to intervention or control groups in Nanjing, China. A multi-component intervention program was implemented within the treatment group, while students in the control group followed their usual health education curriculum without additional intervention.

RESULTS: At baseline, 638 and 544 students were enrolled in the intervention and control group, respectively. The prevalence of excess body weight was 26.8%, with 27.4% in the intervention group and 26.1% in the control group (p=0.61). The mean (SD) BMI and WC was 18.7 (3.0) and 63.0 (9.2) for participants in intervention schools, and 18.5 (2.9) and 63.6 (8.7) for students in control group, separately (p=0.24 and 0.41, respectively). Compared to those who were not aware of what lifestyle/behavior factors were unhealthy, students who were aware of the unhealthy lifestyle/ behavior factors consumed fewer fried snacks (0.46±0.76 serves/week vs 0.65±0.91 serves/week; p<0.01), soft drinks (160±194 ml/week vs 199±227 ml/week; p<0.01), but larger amount of meat (502±429 g/week vs 449±344 g/week; p=0.03), and reported less screen time (214±232 minutes/week vs 252±264 minutes/week; p<0.01). Moreover, there was no difference within physical activity time between these two groups (257±341 minutes/week vs 218±324 minutes/week; p=0.13).

CONCLUSIONS: Main characteristics of participants were balanced at baseline within intervention and control schools, but a gap existed between healthy lifestyle knowledge and actual healthy behavior in students. Trial Registration number: ChiCTR-ERC-11001819.

http://apjcn.nhri.org.tw/server/APJCN/23/1/48.pdf

Trials. 2013 Jul 24;14:232. doi: 10.1186/1745-6215-14-232.

The Good Schools Toolkit to prevent violence against children in Ugandan primary schools: study protocol for a cluster randomised controlled trial.

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BACKGROUND: We aim to evaluate the effectiveness of the Good School Toolkit, developed by Raising Voices, in preventing violence against children attending school and in improving child mental health and educational outcomes.

METHODS/DESIGN: We are conducting a two-arm cluster randomised controlled trial with parallel assignment in Luwero District, Uganda. We will also conduct a qualitative study, a process evaluation and an economic evaluation. A total of 42 schools, representative of Luwero District, Uganda, were allocated to receive the Toolkit plus implementation support, or were allocated to a wait-list control condition. Our main analysis will involve a cross-sectional comparison of the prevalence of past-week violence from school staff as reported by children in intervention and control primary schools at follow-up.At least 60 children per school and all school staff members will be interviewed at follow-up. Data collection involves a combination of mobile phone-based, interviewer-completed questionnaires and paper-and-pen educational tests. Survey instruments include the ISPCAN Child Abuse Screening Tools to assess experiences of violence; the Strengths and Difficulties Questionnaire to measure symptoms of common childhood mental disorders; and word recognition, reading comprehension, spelling, arithmetic and sustained attention tests adapted from an intervention trial in Kenya.

DISCUSSION: To our knowledge, this is the first study to rigorously investigate the effects of any intervention to prevent violence from school staff to children in primary school in a low-income setting. We hope the results will be informative across the African region and in other settings.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23883138/

PLoS One. 2013 Jul 16;8(7):e65775. doi: 10.1371/journal.pone.0065775. Print 2013.

The Support to Rural India's Public Education System (STRIPES) trial: a cluster randomised controlled trial of supplementary teaching, learning material and material support.

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BACKGROUND: The aim of the STRIPES trial was to assess the effectiveness of providing supplementary, remedial teaching and learning materials (and an additional 'kit' of materials for girls) on a composite of language and mathematics test scores for children in classes two, three and four in public primary schools in villages in the Nagarkurnool division of Andhra Pradesh, India.

METHODS: **STRIPES was a cluster randomised trial in which 214 villages were allocated either to the supplementary teaching intervention (n = 107) or to serve as controls (n = 107). 54 of the intervention villages were further randomly allocated to receive additional kit for girls.** The study was not blinded. Analysis was conducted on the intention to treat principle, allowing for clustering.

RESULTS: **Composite test scores were significantly higher in the intervention group (107 villages; 2364 children) than in the control group (106 villages; 2014 children) at the end of the trial (mean difference on a percentage scale 15.8; 95% CI 13.1 to 18.6; p<0.001; 0.75 Standard Deviation (SD) difference).** Composite test scores were not significantly different in the 54 villages (614 girls) with the additional kits for girls compared to the 53 villages (636 girls) without these kits at the end of the trial (mean difference on a percentage scale 0.5; 95% CI -4.34 to 5.4; p = 0.84). The cost per 0.1 SD increase in composite test score for intervention without kits is Rs. 382.97 (£4.45, $7.13), and Rs.480.59 (£5.58, $8.94) for the intervention with kits.

CONCLUSIONS:
A 18 month programme of supplementary remedial teaching and learning materials had a substantial impact on language and mathematics scores of primary school students in rural Andhra Pradesh, yet providing a 'kit' of materials to girls in these villages did not lead to any measured additional benefit.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23874383/

Trials. 2013 Aug 16;14:259. doi: 10.1186/1745-6215-14-259.

Evaluating a community-based early childhood education and development program in Indonesia: study protocol for a pragmatic cluster randomized controlled trial with supplementary matched control group.

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BACKGROUND: This paper presents the study protocol for a pragmatic cluster randomized controlled trial (RCT) with a supplementary matched control group. The aim of the trial is to evaluate a community-based early education and development program launched by the Government of Indonesia. The program was developed in collaboration with the World Bank with a total budget of US$127.7 million, and targets an estimated 738,000 children aged 0 to 6

years living in approximately 6,000 poor communities. **The aim of the program is to increase access to early childhood services with the secondary aim of improving school readiness.**

METHODS/DESIGN: The study is being conducted across nine districts. The baseline survey contained 310 villages, of which 100 were originally allocated to the intervention arm, 20 originally allocated to a 9-month delay staggered start, 100 originally allocated to an 18-month delay staggered start and 90 allocated to a matched control group (no intervention). The study consists of two cohorts, one comprising children aged 12 to 23 months and the other comprising children aged 48 to 59 months at baseline. **The data collection instruments include child observations and task/game-based assessments as well as a questionnaire suite, village head questionnaire, service level questionnaires, household questionnaire, and child caretaker questionnaire.** The baseline survey was conducted from March to April 2009, midline was conducted from April to August 2010 and endline conducted early 2013. The resultant participation rates at both the district and village levels were 90%. At the child level, the participation rate was 99.92%. The retention rate at the child level at midline was 99.67%.

DISCUSSION: This protocol paper provides a detailed record of the trial design including a discussion regarding difficulties faced with compliance to the randomization, compliance to the dispersion schedule of community block grants, and procurement delays for baseline and midline data collections. Considering the execution of the program and the resultant threats to the study, we discuss our analytical plan and intentions for endline data collection.

TRIALS REGISTRATION: Current Controlled Trials ISRCTN76061874.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23953975/

Skin disease

Indian Dermatol Online J. 2013 Jul;4(3):180-4. doi: 10.4103/2229-5178.115511.

To evaluate the efficacy and safety of "RV2427B" cream in Irritant dermatitis care.

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BACKGROUND:
The treatment of various irritant dermatitis involves the elimination of the casual or favoring factor, the control of aggravating factors, and administration of topical agents. Even though corticosteroids are extensively used in these conditions to reduce the inflammation, it can also result in undesirable side effects. Hence, there is a need for a non steroidal topical agent to be used in these conditions.

AIMS: To evaluate the efficacy and tolerance of repairing cream RV 2427B in children and adults in irritant dermatitis care.

MATERIALS AND METHODS: In this phase III open labeled, multicenter, non-controlled, non-randomized trial, **irritant dermatitis in children and adults either due to diaper rash,**

pityriasis alba and irritant dermatitis (eczema), perioral dermatitis, perleche or intertrigo were administered; repairing cream RV 2427 B containing a) 4 % zinc oxide, b) 2.5 % dry colloidal oat extract, (c) 0.5 % oat oil, (d) 0.2% copper sulfate, and (e) 0.1 % zinc sulfate to be applied twice-daily in the affected area. The subjects were evaluated on day 7 and day 21 for both efficacy and tolerance and last visit for cosmetic acceptability. The trial was conducted in accordance with the good clinical practices (GCP) after obtaining ethical clearance from respective Institutional Review Boards. Statistical evaluation was by variance analysis and student test for the quantitative variables, chi-square test for the qualitative variables.

RESULTS: Of the 136 enrolled subjects, 95 completed the study. After 21 days of treatment, 84% of the subjects assessed by the investigator and 76% by the self-assessment for the cream found effective. Investigational product was considered to be safe after 7 and 21 days of use.

CONCLUSION: Repairing cream RV 2427 B is effective and safe in the management of irritant dermatitis.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23984228/

Surgical problems

J Med Assoc Thai. 2013 Sep;96 Suppl 4:S61-70.

Comparison of wound dehiscence and parent's satisfaction between spoon/syringe feeding and breast/bottle feeding in patients with cleft lip repair.

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BACKGROUND: Cleft lip and cleft palate are the most common craniofacial anomalies affecting approximately 2.49 of every 1,000 children born in North-east of Thailand. Srinagarind Hospital has 100-150 cases of cleft lip each year. Children with cleft lip and palate need surgical procedures as soon as possible. After lip repair the normal recommendation is not using bottle or breast feeding for 2 weeks to avoid tension at the sutured area during sucking and possible cause of wound dehiscence. So this is quite complicated for the parents, and patients feel frustrated, cry, and move their head around, because of hunger which cannot easily be satisfied. Previous research found that sucking does not cause wound dehiscence, but mentioned no detail about severity of cleft.

OBJECTIVE: Primary objective is to compare surgical wound dehiscence between breast feeding/bottle and spoon/syringe feeding after lip repair.

MATERIAL AND METHOD: This is an experimental study: non-inferiority trials study. The population is the patients with cleft lip who underwent lip repair in Inpatient Department 3C, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. The study period is during May 2010-February 2013. **The total sample size in the present study is 192 participants, 96 cases breast/bottle feeding, 96 cases spoon/syringe feeding.** The wound dehiscence rate was analyzed by Z-test. Parents'satisfaction is a qualitative data and was analyzed through content analysis.

RESULTS: **No statistical significant diference between breast/bottle and spoon/syringe groups (p-value = 0.320, 95% confidence interval -0.031-0.010). Parents were more satisfied to feed children by breast/bottle and patients were more relaxed with breast/bottle feeding.**

CONCLUSION: **Breast/bottle feeding and syringe/spoon feeding have the same result on the surgical wound. Breast/bottle feeding are not causes of wound dehiscence.**

Afr J Paediatr Surg. 2013 Jul-Sep;10(3):235-8. doi: 10.4103/0189-6725.120889.

Preoperative bowel preparation in children: polyethylene glycol versus normal saline.

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BACKGROUND: Colorectal surgeries frequently require bowel preparation. In children, this is usually performed using normal saline, which is very cumbersome and causes unnecessary discomfort. This study compared polyethylene glycol (PEG) with normal saline for preoperative bowel preparation in children.

PATIENTS AND METHODS: Thirty patients, admitted in the Department of Paediatric Surgery, Rajindra Hospital, Patiala, for colonic and colorectal surgical procedures, were divided into two groups, I (PEG) and II (NS), randomly for bowel preparation with PEG and normal saline, respectively.

RESULTS: **It was found that there was no significant difference in the quality of preparation (P > 0.05), but PEG use was found to be easier, more comfortable and acceptable for the patients, their relatives and the hospital staff.** Overall, complications are significantly lesser for PEG preparation (P < 0.05). There was no significant difference in the overall cost.

CONCLUSION: Thus, it can be inferred that PEG may be a safe, cost-effective and acceptable option for large bowel preparation.

http://www.afrjpaedsurg.org/temp/AfrJPaediatrSurg103235-2527151_070111.pdf

J Pediatr Urol. 2013 Oct;9(5):675-82. doi: 10.1016/j.jpurol.2012.08.001. Epub 2012 Nov 2.

Parental evaluation of postoperative outcome of circumcision with Plastibell or conventional dissection by dorsal slit technique: a randomized controlled trial.

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AIM: To evaluate and compare parental satisfaction after Plastibell and conventional dissection circumcision.

METHODS: **198 children were randomly and equally allocated to two groups (PD: Plastibell and CDS: dissection) for circumcision.** Follow-up was done at 7th, 15th and 90th day after surgery. Written questionnaires were given to parents at the time of discharge to complete and return at the 15th and 90th day follow-up visits.

RESULTS: Both groups were balanced with respect to various demographic factors, indications for surgery and Kayaba's classification of the prepuce. Surgical duration was significantly shorter for the PD as compared to the CDS group (5.91 ± 1.74 min vs. 23.52 ± 5.94 min; $p < 0.0001$ H.S.). Swelling, dysuria and infection were the prominent problems reported in both groups in the first 7 days. The Plastibell separated earlier in younger children ($p < 0.0001$). Postoperatively, children in the PD group required 2.79 fold more analgesic than those in the CDS group. 97.9% of parents in the PD group and 80.2% of parents in the CDS group claimed satisfactory aesthetic results. The PD group parents were statistically significantly more concerned about swelling.

CONCLUSIONS: **Plastibell use has comparable outcomes to the conventional dissection technique for paediatric circumcision and has an obvious advantage of shorter surgical duration. However, it is less comfortable in the postoperative period due to swelling, and requires greater use of analgesics.**

J Neurosurg Pediatr. 2014 Feb;13(2):140-4. doi: 10.3171/2013.11.PEDS13394. Epub 2013 Dec 6.

Effectiveness of the Bactiseal Universal Shunt for reducing shunt infection in a sub-Saharan African context: a retrospective cohort study in 160 Ugandan children.

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OBJECTIVES: Antibiotic-impregnated shunts have yet to find widespread use in the developing world, largely due to cost. Given potential differences in the microbial spectrum, their effectiveness in preventing shunt infection for populations in low-income countries may differ and has not been demonstrated. This study is the first to compare the efficacy of a Bactiseal shunt system with a non-antibiotic-impregnated system in a developing country.

METHODS: **The Bactiseal Universal Shunt (BUS) was placed in 80 consecutive Ugandan children who required a shunt. In this retrospective cohort study, the outcome for that group was compared with the outcome for the immediately preceding 80 consecutive children in whom a Chhabra shunt had been placed. The primary end points were shunt failure, shunt infection, and death.** Shunt survival was analyzed using the Kaplan-Meier method. Significance of differences between groups was tested using the log-rank test, chi-square analysis, Fisher's exact test, and t-test.

RESULTS: There was no difference between groups in regard to age, sex, or etiology of hydrocephalus. Mean follow-up for cases of nonfailure was 7.6 months (median 7.8 months, interquartile range 6.5-9.5 months). There was no significant difference between groups for any end point. **The BUS group had fewer infections (4 vs 11), but the difference was not significant (p = 0.086, log-rank test). Gram-positive cocci were the most common culturable pathogens in the Chhabra group, while the only positive culture in the BUS group was a gram-negative rod.**

CONCLUSIONS: These results provide equipoise for a randomized controlled trial in the same population and this has been initiated. It is possible that the observed trends may become significant in a larger study. The more complex task will involve determining not only the efficacy, but also the cost-effectiveness of using antibiotic-impregnated shunt components in limited-resource settings.

Comment

As in many small controlled trials published this year, type II errors are commonly made. P-values are mistakenly interpreted as indicating "equipoise", "non-inferiority" or "no difference" when the trial is under-powered and the results inconclusive.

J Plast Reconstr Aesthet Surg. 2013 Sep;66(9):e239-45. doi: 10.1016/j.bjps.2013.05.001. Epub 2013 Jun 1.

Tensor tenopexy: a clinical study to assess its effectiveness in improving Eustachian tube function and preventing hearing loss in patients with cleft palate.

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There is a consensus about the occurrence of otitis media in children with cleft palate before repair. However, controversy continues regarding the recovery of Eustachian tube function and level of hearing loss in the patients after cleft palate repair. Levator sling palatoplasty is an important component of the cleft repair. Most surgeons would routinely transect the tensor tendon (tensor tenotomy) during the course of palatoplasty. However, this procedure may pose a risk to Eustachian tube function. Some authorities feel that addition of tensor tenopexy during palatoplasty would maintain the Eustachian tube in an open conformation, thereby improving middle ear ventilation. The present study assesses the effectiveness of tensor tenopexy in improving Eustachian tube function and preventing hearing loss in cleft palate patients treated with palatoplasty. A prospective randomised controlled trial was conducted in the Department of Plastic Surgery at a tertiary care institute in India. **A total of 17 children in the age group of 9-**

24 months were assigned to one of two groups: palatoplasty with either tensor tenotomy (n = 8) or tensor tenotomy with tensor tenopexy (n = 9). All patients were subjected to tympanometry, otoscopy and brainstem evoked response audiometry before surgery and at 3, 6, 9 and 12 months after surgery. Of these, 52.9% of patients already had hearing loss at the time of presentation. Hearing loss and middle ear effusion persisted even after palatoplasty. **There was no significant difference in hearing loss and middle ear effusion between the two groups of patients.** Thus, tensor tenopexy was not found to be helpful in maintaining Eustachian tube function or preventing hearing loss in cleft palate patients. However, further long-term studies are needed to confirm this study.

Comment
Ditto (8 and 9 patients in each group)

Tuberculosis

Lancet. 2013 Oct 5;382(9899):1183-94. doi: 10.1016/S0140-6736(13)61131-9. Epub 2013 Aug 1.

Effect of household and community interventions on the burden of tuberculosis in southern Africa: the ZAMSTAR community-randomised trial.

Ayles H[1], Muyoyeta M, Du Toit E, Schaap A, Floyd S, Simwinga M, Shanaube K, Chishinga N, Bond V, Dunbar R, De Haas P, James A, Gey van Pittius NC, Claassens M, Fielding K, Fenty J, Sismanidis C, Hayes RJ, Beyers N, Godfrey-Faussett P; ZAMSTAR team.
Collaborators (36)
Banda G, Bwalya G, Chabalala M, Cornelius J, Handima N, Kapaku K, Kobi B, Muludyang F, Mwangelwa B, Ndhlovu M, Ngoma N, Nikani D, Nota A, Pedro C, Sattar S, Sibande N, Sichalwe P, Speelman E, Tsamwa D, Van Zyl L, Yang B, Cheeba M, Chizeni B, Jaffer A, Jordaan A, Kosloff B, Mbulo G, Moyo M, Mwamba M, Mwanza W, van Helden P, Cogill D, Jacobs T, Kasese N, Lawrence K, Milimo D.

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BACKGROUND: Southern Africa has had an unprecedented increase in the burden of tuberculosis, driven by the HIV epidemic. The Zambia, South Africa Tuberculosis and AIDS Reduction (ZAMSTAR) trial examined two public health interventions that aimed to reduce the burden of tuberculosis by facilitating either rapid sputum diagnosis or integrating tuberculosis and HIV services within the community.

METHODS: ZAMSTAR was a community-randomised trial done in Zambia and the Western Cape province of South Africa. Two interventions, community-level enhanced tuberculosis case-finding (ECF) and household level tuberculosis-HIV care, were implemented between Aug 1, 2006, and July 31, 2009, and assessed in a 2×2 factorial design between Jan 9, 2010, and Dec 6, 2010. *All communities had a strengthened tuberculosis-HIV programme implemented in participating health-care centres.* **24 communities, selected according to population size and tuberculosis notification rate, were randomly allocated to one of four study groups using a**

randomisation schedule stratified by country and baseline prevalence of tuberculous infection: group 1 strengthened tuberculosis-HIV programme at the clinic alone; group 2, clinic plus ECF; group 3, clinic plus household intervention; and group 4, clinic plus ECF and household interventions. The primary outcome was the prevalence of culture-confirmed pulmonary tuberculosis in adults (≥18 years), defined as Mycobacterium tuberculosis isolated from one respiratory sample, measured 4 years after the start of interventions in a survey of 4000 randomly selected adults in each community in 2010. The secondary outcome was the incidence of tuberculous infection, measured using tuberculin skin testing in a cohort of schoolchildren, a median of 4 years after a baseline survey done before the start of interventions. This trial is registered, number ISRCTN36729271.

FINDINGS: Prevalence of tuberculosis was evaluated in 64,463 individuals randomly selected from the 24 communities; 894 individuals had active tuberculosis. Averaging over the 24 communities, the geometric mean of tuberculosis prevalence was 832 per 100,000 population. **The adjusted prevalence ratio for the comparison of ECF versus non-ECF intervention groups was 1·09 (95% CI 0·86-1·40) and of household versus non-household intervention groups was 0·82 (0·64-1·04).** The incidence of tuberculous infection was measured in a cohort of 8809 children, followed up for a median of 4 years; the adjusted rate ratio for ECF versus non-ECF groups was 1·36 (95% CI 0·59-3·14) and for household versus non-household groups was 0·45 (0·20-1·05).

INTERPRETATION: **Although neither intervention led to a statistically significant reduction in tuberculosis, two independent indicators of burden provide some evidence of a reduction in tuberculosis among communities receiving the household intervention.** By contrast the ECF intervention had no effect on either outcome.

http://linkinghub.elsevier.com/retrieve/pii/S0140-6736(13)61131-9

Cochrane Database Syst Rev. 2014 Jan 28;1:CD007953. doi: 10.1002/14651858.CD007953.pub2.

Intermittent versus daily therapy for treating tuberculosis in children.

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BACKGROUND: Childhood tuberculosis (TB) is a neglected global public health problem. **Short treatment courses with rifampicin-containing anti-TB drugs given daily for six-months cure over 90% of infected children, but poor adherence reduces treatment success. Intermittent, short-course anti-TB regimens, given two or three times a week under direct observation, are associated with higher adherence in observational studies; but how they compare with daily treatment in relation to cure is unclear.** Current international and national recommendations differ on use of intermittent regimens to treat TB in children.

OBJECTIVES: **To compare the efficacy and safety of intermittent, short-course anti-TB regimens (twice- or thrice-weekly) with daily short-course anti-TB regimens in treating childhood TB.**

SEARCH METHODS: We searched the Cochrane Infectious Disease Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, clinical trials registries, regional databases, conference proceedings, and references

without language restrictions up to 30 May 2013; and contacted experts for relevant published, unpublished, and on-going trials.

SELECTION CRITERIA: Randomized controlled trials (RCTs) and quasi-RCTs of children aged 15 years or younger, diagnosed with TB (according to the World Health Organization diagnostic categories 1, 2, or 3), who were treated with intermittent twice-weekly or thrice-weekly, short-course anti-TB regimens compared to daily short-course anti-TB treatment regimens. All regimens had to contain rifampicin for at least the first two months.

DATA COLLECTION AND ANALYSIS: The review authors independently screened and selected trials, assessed risk of bias, and extracted data. We sought clarifications from trial authors. We pooled relative risks with their 95% confidence intervals and used a random-effects model where there was significant heterogeneity. We assessed overall evidence-quality using the GRADE approach.

MAIN RESULTS: **We included four trials published between 1996 to 2000 that randomized 563 children (465 evaluable) aged five months to 15 years to intermittent twice-weekly versus daily anti-TB treatment.** Two trials were from India, one from South Africa, and one from Turkey. All trials used rifampicin and isoniazid, three trials used pyrazinamide, and one trial used streptomycin. The drug combination, and the duration of intermittent and daily treatments differed between trials, and no trials used drug combinations and schedules currently recommended for childhood TB. No trial reported if any child was HIV-positive. **In comparisons of twice-weekly versus daily anti-TB treatment regimens, the trials did not detect differences in the number of patients cured, but trials were small, and the comparator regimens were not standard (four trials, 465 children; very low quality evidence).** Trials were underpowered to provide estimates for death (two trials, 213 participants, very low quality evidence), relapse (one trial, 214 participants,very low quality evidence), and treatment limiting adverse events (four trials, 441 participants, very low quality evidence). Reported adherence to treatment was similar (87% versus 84%; four trials, 458 children, very low quality evidence). We did not find trials comparing the commonly used thrice-weekly anti-TB short-course regimen with the daily treatment regimen.

AUTHORS' CONCLUSIONS: Trials conducted to date are insufficient to support or refute the use of intermittent twice- or thrice-weekly, short-course treatment regimens over daily short-course treatment in children with TB. Further randomized trials conducted in high TB-transmission settings will help inform policy and practice.

http://onlinelibrary.wiley.com/store/10.1002/14651858.CD007953.pub2/asset/CD007953.pdf?v=1&t=hxd436ph&s=64efae81c822a61d5be767ca5027f72d8d508281

Comment

WHO's current recommendation is as follows:

- *Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy*

- *New patients with pulmonary TB may receive a daily intensive phase followed by a three times weekly continuation phase: 2HRZE/4(HR)$_3$, provided that EACH DOSE IS DIRECTLY OBSERVED and the patient is NOT living with HIV or living in an HIV-prevalent setting*

That's a lot of ifs, so in most cases and in most settings, daily continuation-phase treatment is best. http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf?ua=1

Int J Tuberc Lung Dis. 2013 Nov;17(11):1383-8. doi: 10.5588/ijtld.13.0348.

Role of the QuantiFERON®-TB Gold In-Tube test in the diagnosis of intrathoracic childhood tuberculosis.

Lodha R[1], Mukherjee A, Saini D, Saini S, Singh V, Singh S, Grewal HM, Kabra SK; Delhi TB Study Group.
Collaborators (20)
Arya T, Bhatnagar S, Chandra J, Dutta AK, Doherty TM, Friis H, Grewal HM, Hesseling AC, Kabra SK, Lodha R, Marais B, Mukherjee A, Parashar D, Prajapati S, Purohit K, Saini D, Saini S, Singh RR, Singh S, Singh V.

[1]Department of Paediatrics, All India Institute of Medical Sciences (AIIMS), New Delhi, India.

SETTING: Tertiary care hospitals in India.

OBJECTIVE: To compare the performance of the QuantiFERON®-TB Gold In-Tube test (QFT-GIT) with that of the tuberculin skin test (TST) in the diagnosis of intrathoracic childhood tuberculosis (TB).

METHODS: **Children with intrathoracic TB were enrolled in a randomised controlled trial studying micronutrient supplementation in intrathoracic TB.** They underwent TST and QFT-GIT before starting daily anti-tuberculosis treatment.

RESULTS: Of 362 children (median age 115.5 months, IQR 73-144, 55% girls) enrolled in the study, microbiological confirmation of TB was obtained in 128 (35%). **The TST was positive in 337 (93%, 95%CI 90-95.5) and QFT-GIT in 297 (82%, 95%CI 77.8-85.6).** Sensitivity of TST and QFT-GIT in culture-confirmed TB cases was respectively 90.5% (95%CI 84.1-94.5) and 82.6% (95% CI 74.9-88.4). QFT-GIT positivity rate correlated with TST induration ($P < 0.001$). TST was influenced by the disease spectrum ($P = 0.004$) and the age of the children ($P = 0.002$); QFT-GIT remained unaffected by these factors. Bacille Calmette-Guérin immunisation status, weight-for-age Z-scores and microbiological confirmation of Mycobacterium tuberculosis did not influence the performance of either test.

CONCLUSION: In high-burden countries, QFT-GIT is comparable to TST and offers no added advantage in the diagnosis of childhood intrathoracic TB.

http://openurl.ingenta.com/content/nlm?genre=article&issn=1027-3719&volume=17&issue=11&spage=1383&aulast=Lodha

Comment

WHO released a statement indicating that Quantiferon Gold is not a useful test in high TB burden developing countries, as it doesn't distinguish infection from disease. GeneXpert on the other hand does and has been the subject of many studies in the last few years.

Vaccines and immunization

Cholera vaccine

Lancet Infect Dis. 2013 Dec;13(12):1050-6. doi: 10.1016/S1473-3099(13)70273-1. Epub 2013 Oct 18.

5 year efficacy of a bivalent killed whole-cell oral cholera vaccine in Kolkata, India: a cluster-randomised, double-blind, placebo-controlled trial.

Bhattacharya SK[1], Sur D, Ali M, Kanungo S, You YA, Manna B, Sah B, Niyogi SK, Park JK, Sarkar B, Puri MK, Kim DR, Deen JL, Holmgren J, Carbis R, Dhingra MS, Donner A, Nair GB, Lopez AL, Wierzba TF, Clemens JD.

[1]National Institute of Cholera and Enteric Diseases, Kolkata, India; Indian Council of Medical Research, New Delhi, India.

Erratum in
Lancet Infect Dis. 2013 Dec;13(12):1011.

BACKGROUND: Efficacy and safety of a two-dose regimen of bivalent killed whole-cell oral cholera vaccine (Shantha Biotechnics, Hyderabad, India) to 3 years is established, but long-term efficacy is not. We aimed to assess protective efficacy up to 5 years in a slum area of Kolkata, India.

METHODS: In our double-blind, cluster-randomised, placebo-controlled trial, we assessed incidence of cholera in non-pregnant individuals older than 1 year residing in 3933 dwellings (clusters) in Kolkata, India. **We randomly allocated participants, by dwelling, to receive two oral doses of modified killed bivalent whole-cell cholera vaccine or heat-killed Escherichia coli K12 placebo, 14 days apart.** Randomisation was done by use of a computer-generated sequence in blocks of four. The primary endpoint was prevention of episodes of culture-confirmed Vibrio cholerae O1 diarrhoea severe enough for patients to seek treatment in a health-care facility. **We identified culture-confirmed cholera cases among participants seeking treatment for diarrhoea at a study clinic or government hospital between 14 days and 1825 days after receipt of the second dose.** We assessed vaccine protection in a per-protocol population of participants who had completely ingested two doses of assigned study treatment.

FINDINGS: **69 of 31 932 recipients of vaccine and 219 of 34 968 recipients of placebo developed cholera during 5 year follow-up (incidence 2·2 per 1000 in the vaccine group and 6·3 per 1000 in the placebo group). Cumulative protective efficacy of the vaccine at 5 years was 65% (95% CI 52-74; p<0·0001), and point estimates by year of follow-up suggested no evidence of decline in protective efficacy.**

INTERPRETATION: Sustained protection for 5 years at the level we reported has not been noted previously with other oral cholera vaccines. Established long-term efficacy of this vaccine could assist policy makers formulate rational vaccination strategies to reduce overall cholera burden in endemic settings.

http://linkinghub.elsevier.com/retrieve/pii/S1473-3099(13)70273-1

Dengue vaccine

Vaccine. 2013 Dec 2;31(49):5814-21. doi: 10.1016/j.vaccine.2013.10.013. Epub 2013 Oct 14.

Safety and immunogenicity of a tetravalent dengue vaccine in healthy children aged 2-11 years in Malaysia: a randomized, placebo-controlled, Phase III study.

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[1]Department of Pediatrics, Hospital Raja Permaisuri Bainun, Jalan Hospital, Ipoh, Perak, Malaysia. Electronic address: amarhss@gmail.com.

BACKGROUND: Dengue disease is a major public health problem across the Asia-Pacific region for which there is no licensed vaccine or treatment. **We evaluated the safety and immunogenicity of Phase III lots of a candidate vaccine (CYD-TDV) in children in Malaysia.**

METHODS: **In this observer-blind, placebo-controlled, Phase III study, children aged 2-11 years were randomized (4:1) to receive CYD-TDV or placebo at 0, 6 and 12 months.** Primary endpoints included assessment of reactogenicity following each dose, adverse events (AEs) and serious AEs (SAEs) reported throughout the study, and immunogenicity expressed as geometric mean titres (GMTs) and distribution of dengue virus (DENV) neutralizing antibody titres.

RESULTS: 250 participants enrolled in the study (CYD-TDV: n=199; placebo: n=51). **There was a trend for reactogenicity to be higher with CYD-TDV than with placebo post-dose 1 (75.4% versus 68.6%) and post-dose 2 (71.6% versus 62.0%) and slightly lower post-dose 3 (57.9% versus 64.0%).** Unsolicited AEs declined in frequency with each subsequent dose and were similar overall between groups (CYD-TDV: 53.8%; placebo: 49.0%). Most AEs were of Grade 1 intensity and were transient. SAEs were reported by 5.5% and 11.8% of participants in the CYD-TDV and placebo groups, respectively. No deaths were reported. Baseline seropositivity against each of the four DENV serotypes was similar between groups, ranging from 24.0% (DENV-4) to 36.7% (DENV-3). **In the CYD-TDV group, GMTs increased post-dose 2 for all serotypes compared with baseline, ranging from 4.8 (DENV-1) to 8.1-fold (DENV-3). GMTs further increased post-dose 3 for DENV-1 and DENV-2.** Compared with baseline, individual titre increases ranged from 6.1-fold (DENV-1) to 7.96-fold (DENV-3).

CONCLUSIONS: This study demonstrated a satisfactory safety profile and a balanced humoral immune response against all four DENV serotypes for CYD-TDV administered via a three-dose regimen to children in Malaysia.

http://linkinghub.elsevier.com/retrieve/pii/S0264-410X(13)01365-0

Am J Trop Med Hyg. 2013 Dec;89(6):1058-65. doi: 10.4269/ajtmh.13-0304. Epub 2013 Nov 4.

Immunogenicity and safety of a recombinant tetravalent dengue vaccine in children and adolescents ages 9-16 years in Brazil.

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Immunogenicity and safety of a recombinant, live-attenuated, tetravalent dengue disease vaccine (CYD-TDV) was evaluated in children/adolescents in Brazil. In this observer-blind, placebo-controlled, phase II single-center study, children/adolescents (ages 9-16 years) were randomized to receive CYD-TDV or placebo at 0, 6, and 12 months. Immunogenicity was assessed using a 50% plaque neutralization test. Overall, 150 participants were enrolled (CYD-TDV: N = 100; placebo: N = 50). Injection site pain and headache were the most common solicited injection site and systemic reactions. Unsolicited adverse events (AEs) and serious AEs were similar between groups. No serious AEs were vaccine-related. **Geometric mean titers against all dengue virus serotypes increased with CYD-TDV vaccination and were 267, 544, 741, and 432 1/dil for serotypes 1-4, respectively, after dose 3, representing a mean fold increase from baseline of 5, 6, 6, and 20, respectively.** CYD-TDV vaccination elicited a neutralizing antibody response against serotypes 1-4 and was well-tolerated in children/adolescents in a dengue-endemic region.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24189367/

E. coli vaccine

Cochrane Database Syst Rev. 2013 Jul 5;7:CD009029. doi: 10.1002/14651858.CD009029.pub2.

Vaccines for preventing enterotoxigenic Escherichia coli (ETEC) diarrhoea.

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[1]Variation Biotechnologies Inc., Ottawa, Canada.

BACKGROUND: Infection with enterotoxigenic Escherichia coli (ETEC) bacteria is a common cause of diarrhoea in adults and children in developing countries and is a major cause of 'travellers' diarrhoea' in people visiting or returning from endemic regions. A killed whole cell vaccine (Dukoral®), primarily designed and licensed to prevent cholera, has been recommended by some groups to prevent travellers' diarrhoea in people visiting endemic regions. This vaccine contains a recombinant B subunit of the cholera toxin that is antigenically similar to the heat labile toxin of ETEC. This review aims to evaluate the clinical efficacy of this vaccine and other vaccines designed specifically to protect people against diarrhoea caused by ETEC infection.

OBJECTIVES: To evaluate the efficacy, safety, and immunogenicity of vaccines for preventing ETEC diarrhoea.

SEARCH METHODS: We searched the Cochrane Infectious Disease Group Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, LILACS, and http://clinicaltrials.gov up to December 2012.

SELECTION CRITERIA: Randomized controlled trials (RCTs) and quasi-RCTs comparing use of vaccines to prevent ETEC with use of no intervention, a control vaccine (either an inert vaccine or a vaccine normally given to prevent an unrelated infection), an alternative ETEC vaccine, or a different dose or schedule of the same ETEC vaccine in healthy adults and children living in endemic regions, intending to travel to endemic regions, or volunteering to receive an artificial challenge of ETEC bacteria.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed each trial for eligibility and risk of bias. Two independent reviewers extracted data from the included studies and analyzed the data using Review Manager (RevMan) software. We reported outcomes as risk ratios (RR) with 95% confidence intervals (CI). We assessed the quality of the evidence using the GRADE approach.

MAIN RESULTS: Twenty-four RCTs, including 53,247 participants, met the inclusion criteria. Four studies assessed the protective efficacy of oral cholera vaccines when used to prevent diarrhoea due to ETEC and seven studies assessed the protective efficacy of ETEC-specific vaccines. Of these 11 studies, seven studies presented efficacy data from field trials and four studies presented efficacy data from artificial challenge studies. An additional 13 trials contributed safety and immunological data only. The currently available, oral cholera killed whole cell vaccine (Dukoral®) was evaluated for protection of people against 'travellers' diarrhoea' in a single RCT in people arriving in Mexico from the USA. We did not identify any statistically significant effects on ETEC diarrhoea or all-cause diarrhoea (one trial, 502 participants, low quality evidence).Two earlier trials, one undertaken in an endemic population in Bangladesh and one undertaken in people travelling from Finland to Morocco, evaluated a precursor of this vaccine containing purified cholera toxin B subunit rather than the recombinant subunit in Dukoral®. Short term protective efficacy against ETEC diarrhoea was demonstrated, lasting for around three months (RR 0.43, 95% CI 0.26 to 0.71; two trials, 50,227 participants). This vaccine is no longer available. ETEC vaccinesAn ETEC-specific, killed whole cell vaccine, which also contains the recombinant cholera toxin B-subunit, was evaluated in people travelling from the USA to Mexico or Guatemala, and from Austria to Latin America, Africa, or Asia. We did not identify any statistically significant differences in ETEC-specific diarrhoea or all-cause diarrhoea (two trials, 799 participants), and the vaccine was associated with increased vomiting (RR 2.0, 95% CI 1.16 to 3.45; nine trials, 1528 participants). The other ETEC-specific vaccines in development have not yet demonstrated clinically important benefits.

AUTHORS' CONCLUSIONS: **There is currently insufficient evidence from RCTs to support the use of the oral cholera vaccine Dukoral® for protecting travellers against ETEC diarrhoea.** Further research is needed to develop safe and effective vaccines to provide both short and long-term protection against ETEC diarrhoea.

http://onlinelibrary.wiley.com/store/10.1002/14651858.CD009029.pub2/asset/CD009029.pdf?v=1&t=hxd46kso&s=08ba6279be8c90509ee4c6d043e6a7dc48607dd7

Enterovirus vaccine

N Engl J Med. 2014 Feb 27;370(9):829-37. doi: 10.1056/NEJMoa1303224.

An inactivated enterovirus 71 vaccine in healthy children.

Li R[1], Liu L, Mo Z, Wang X, Xia J, Liang Z, Zhang Y, Li Y, Mao Q, Wang J, Jiang L, Dong C, Che Y, Huang T, Jiang Z, Xie Z, Wang L, Liao Y, Liang Y, Nong Y, Liu J, Zhao H, Na R, Guo L, Pu J, Yang E, Sun L, Cui P, Shi H, Wang J, Li Q.

[1]From Guangxi Province Center for Disease Control and Prevention, Nanning (R.L., Z.M., Y. Li, T.H., Y.N.), Yunnan Key Laboratory of Vaccine Research and Development on Severe Infectious Diseases, Institute of Medical Biology, Chinese Academy of Medical Sciences and Peking Union Medical College, Kunming (L.L., Y.Z., Jingjing Wang, L.J., C.D., Y.C., Z.X., L.W., Y. Liao, Y. Liang, J.L., H.Z., R.N., L.G., J.P., E.Y., L.S., P.C., H.S., Q.L.), Key Laboratory Medical Molecular Virology, Ministries of Education and Health, and the Institutes of Biomedical Science, Shanghai Medical College, Fudan University, Shanghai (X.W.), Department of Health Statistics, Fourth Military Medical University, Xi'an (J.X., Z.J.), and National Institutes for Food and Drug Control, Beijing (Z.L., Q.M., Junzhi Wang) - all in China.

BACKGROUND: Enterovirus 71 (EV71) is a major cause of hand, foot, and mouth disease in children and may be fatal. A vaccine against EV71 is needed.

METHODS: We conducted a randomized, double-blind, placebo-controlled phase 3 trial involving healthy children 6 to 71 months of age in Guangxi Zhuang Autonomous Region, China. Two doses of an inactivated EV71 vaccine or placebo were administered intramuscularly, with a 4-week interval between doses, and children were monitored for up to 11 months. The primary end point was protection against hand, foot, and mouth disease caused by EV71.

RESULTS: A total of 12,000 children were randomly assigned to receive vaccine or placebo. Serum neutralizing antibodies were assessed in 549 children who received the vaccine. The seroconversion rate was 100% 4 weeks after the two vaccinations, with a geometric mean titer of 170.6. **Over the course of two epidemic seasons, the vaccine efficacy was 97.4% (95% confidence interval [CI], 92.9 to 99.0) according to the intention-to-treat analysis and 97.3% (95% CI, 92.6 to 99.0) according to the per-protocol analysis.** Adverse events, such as fever (which occurred in 41.6% of the participants who received vaccine vs. 35.2% of those who received placebo), were significantly more common in the week after vaccination among children who received the vaccine than among those who received placebo.

CONCLUSIONS: **The inactivated EV71 vaccine elicited EV71-specific immune responses and protection against EV71-associated hand, foot, and mouth disease**. (Funded by the National Basic Research Program and others; ClinicalTrials.gov number, NCT01569581.).

N Engl J Med. 2014 Feb 27;370(9):818-28. doi: 10.1056/NEJMoa1304923.

Efficacy, safety, and immunogenicity of an enterovirus 71 vaccine in China.

Zhu F[1], Xu W, Xia J, Liang Z, Liu Y, Zhang X, Tan X, Wang L, Mao Q, Wu J, Hu Y, Ji T, Song L, Liang Q, Zhang B, Gao Q, Li J, Wang S, Hu Y, Gu S, Zhang J, Yao G, Gu J, Wang X, Zhou Y, Chen C, Zhang M, Cao M, Wang J, Wang H, Wang N.

[1]From the Jiangsu Provincial Center for Disease Control and Prevention, Nanjing (F.Z., X.Z., Yuemei Hu, Q.L., J.L., S.W., H.W.); National Institutes for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention (W.X., X.T., T.J., B.Z.),

National Institutes for Food and Drug Control (Z.L., Q.M., J. Wang), and Sinovac Biotech (Y.L., J. Wu, L.S., Q.G., Yuansheng Hu, N.W.), Beijing; the Fourth Military Medical University, Xi'an (J.X., L.W.); Sheyang County Center for Disease Control and Prevention, Yancheng City (S.G., J.G., C.C.); Ganyu County Center for Disease Control and Prevention, No. 98, Lianyungang City (J.Z., X.W., M.Z.); and Taixing County Center for Disease Control and Prevention, No. 224, Taizhou City (G.Y., Y.Z., M.C.) - all in China.

BACKGROUND: Enterovirus 71 (EV71) is one of the major causative agents of outbreaks of hand, foot, and mouth disease or herpangina worldwide. This phase 3 trial was designed to evaluate the efficacy, safety, and immunogenicity of an EV71 vaccine.

METHODS: **We conducted a randomized, double-blind, placebo-controlled, multicenter trial in which 10,007 healthy infants and young children (6 to 35 months of age) were randomly assigned in a 1:1 ratio to receive two intramuscular doses of either EV71 vaccine or placebo, 28 days apart.** The surveillance period was 12 months. The primary end point was the occurrence of EV71-associated hand, foot, and mouth disease or herpangina.

RESULTS: During the 12-month surveillance period, EV71-associated disease was identified in 0.3% of vaccine recipients (13 of 5041 children) and 2.1% of placebo recipients (106 of 5028 children) in the intention-to-treat cohort. **The vaccine efficacy against EV71-associated hand, foot, and mouth disease or herpangina was 94.8% (95% confidence interval [CI], 87.2 to 97.9; P<0.001) in this cohort.** Vaccine efficacies against EV71-associated hospitalization (0 cases vs. 24 cases) and hand, foot, and mouth disease with neurologic complications (0 cases vs. 8 cases) were both 100% (95% CI, 83.7 to 100 and 42.6 to 100, respectively). Serious adverse events occurred in 111 of 5044 children in the vaccine group (2.2%) and 131 of 5033 children in the placebo group (2.6%). In the immunogenicity subgroup (1291 children), an anti-EV71 immune response was elicited by the two-dose vaccine series in 98.8% of participants at day 56. An anti-EV71 neutralizing antibody titer of 1:16 was associated with protection against EV71-associated hand, foot, and mouth disease or herpangina.

CONCLUSIONS: **The EV71 vaccine provided protection against EV71-associated hand, foot, and mouth disease or herpangina in infants and young children**. (Funded by Sinovac Biotech; ClinicalTrials.gov number, NCT01507857.).

Hepatitis A vaccine

Hum Vaccin Immunother. 2013 Jul;9(7):1460-5. doi: 10.4161/hv.24366. Epub 2013 Apr 9.

Comparison of immunogenicity between inactivated and live attenuated hepatitis A vaccines: a single-blind, randomized, parallel-group clinical trial among children in Xinjiang Uighur Autonomous Region, China.

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OBJECTIVES: **To compare immunogenicity among an inactivated hepatitis A vaccine (Healive(®)) with one-dose and two-dose regimens, and three kinds of live attenuated vaccines in children.**

METHODS: A single-blind, randomized, parallel-group clinical trial was conducted among healthy children aged 1.5-6 y in Xinjiang Uighur Autonomous Region, China. Subjects were randomly assigned to 5 groups. **Two groups were administered one-dose or two-dose inactivated vaccine and the remaining groups were immunized with one of three kinds of attenuated vaccines, respectively.** Serum samples were collected at 6- and 12-mo follow-ups. Anti-HAV IgG was measured with a microparticle enzyme immunoassay.

RESULTS: No significant differences were observed in seroconversion rates (seroprotection rates) among the five groups at 6 or 12 mo ($p>0.05$). The geometric mean concentration (GMC) of anti-HAV IgG was significantly higher in the two-dose Healive(®) group than in the one-dose Healive(®) group and the attenuated vaccine groups at 12 mo (932.4 vs. 112.7, 135.8, 203.3, 212.8 mIU/ml, respectively, $p<0.05$). In the one-dose Healive(®) group, the GMC was significantly lower than that in the attenuated vaccine B and C groups at 6 mo (152.6 vs. 212, 204 mIU/ml, $p<0.05$) and at 12 mo (112.7 vs. 203.3, 212.8, $p<0.05$), but was similar to the attenuated vaccine A group at 12 mo (112.7 vs. 135.8 mIU/ml, $p>0.05$). The GMCs were significantly higher in the 1-2 y of age group than in the 3-6 y of age group for all types of vaccines except the attenuated vaccine C ($p<0.05$) at 12 mo.

CONCLUSIONS: A higher GMC of anti-HAV IgG was induced in the two-dose Healive(®) than in the one-dose and the attenuated vaccines at 12 mo. The attenuated vaccine B or C produced higher GMCs than the one-dose Healive(®) at 6-12 mo after vaccination.

http://www.landesbioscience.com/journals/hv/abstract.php?id=24366

Hepatitis B vaccine

J Viral Hepat. 2013 Nov;20(11):801-10. doi: 10.1111/jvh.12102. Epub 2013 Apr 23.

Hepatitis B vaccination with or without hepatitis B immunoglobulin at birth to babies born of HBsAg-positive mothers prevents overt HBV transmission but may not prevent occult HBV infection in babies: a randomized controlled trial.

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Vertical transmission of Hepatitis B virus HBV can result in a state of chronic HBV infection and its complications. HBV vaccination with or without hepatitis B immunoglobulin (HBIG) prevents transmission of overt infection to the babies. However, whether it also prevents occult HBV infection in babies is not known. Consecutive pregnant women of any gestation found to be HBsAg positive were followed till delivery, and their babies were included in the study. **Immediately after delivery, babies were randomized to receive either HBIG or placebo in addition to recombinant HBV vaccine (at 0, 6, 10 and 14 weeks).** The primary end-point of the study, assessed at 18 weeks of age, was remaining free of any HBV infection (either overt or

occult) plus the development of adequate immune response to vaccine. The babies were further followed up for a median of 2 years of age to determine their eventual outcome. Risk factors for HBV transmission and for poor immune response in babies were studied. **Of the 283 eligible babies, 259 were included in the trial and randomized to receive either HBIG (n=128) or placebo (n=131) in addition to recombinant HBV vaccine.** Of the 222 of 259 (86%) babies who completed 18 weeks of follow-up, only 62/222 (28%) reached primary end-point. Of the remaining, 6/222 (3%) developed overt HBV infection, 142/222 (64%) developed occult HBV infection, and 12/222 (5%) had no HBV infection but had poor immune response. **All 6 overt infections occurred in the placebo group (P=0.030), while occult HBV infections were more common in the HBIG group (76/106 [72%] vs. 66/116 [57%]; P=0.025).** This may be due to the immune pressure of HBIG. There was no significant difference between the two groups in frequency of babies developing poor immune response or those achieving primary end-point. The final outcome of these babies at 24 months of age was as follows: overt HBV infection 4%, occult HBV infection 42%, no HBV infection but poor immune response 8% and no HBV infection with good immune response 28%. Women who were anti-HBe positive were a low-risk group, and their babies were most likely to remain free of HBV infection (occult or overt) and had good immune response to the vaccine. Maternal HBeAg-positive status and negativity for anti-HBe predicted not only overt but also any infection (both overt and occult) in babies. In addition, high maternal HBV DNA and treatment with vaccine alone were significant factors for overt HBV infection in babies. **The current practice of administration of vaccine with HBIG at birth to babies born of HBsAg-positive mothers is not effective in preventing occult HBV infection in babies, which may be up to 40%.** Because the most important risk factors for mother-to-baby transmission of HBV infection are the replicative status and high HBV DNA level in mothers; it will be worthwhile investigating the role of antivirals and HBIG administration during pregnancy to prevent mother-to-child transmission of HBV infection.

HPV vaccine

Vaccine. 2013 Nov 19;31(48):5745-53. doi: 10.1016/j.vaccine.2013.09.032. Epub 2013 Oct 1.

Safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-positive women in South Africa: a partially-blind randomised placebo-controlled study.

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In developing countries, risk of human papillomavirus (HPV) infection may be increased by the high prevalence of human immunodeficiency virus (HIV) infection. We evaluated the **safety and immunogenicity of the HPV-16/18 AS04-adjuvanted vaccine in HIV-infected women in South Africa. Asymptomatic HIV-positive women aged 18-25 years (N=120) were stratified by $CD4^+$ T-cell count and randomised (1:1) to receive HPV-16/18 vaccine (Cervarix®; GlaxoSmithKline Vaccines) or placebo (Al[OH]3) at 0, 1 and 6 months** (double-blind). HIV-negative women (N=30) received HPV-16/18 vaccine (open label). Anti-HPV-16/18 antibody and $CD4^+$ T-cell responses, $CD4^+$ T-cell count, HIV viral load, HIV

clinical stage and safety were evaluated for 12 months. The safety and reactogenicity profile of the HPV-16/18 vaccine was comparable in HIV-positive and HIV-negative women. **Irrespective of baseline HPV status, all HIV-positive and HIV-negative women who received the HPV-16/18 vaccine were seropositive for both HPV-16 and HPV-18 after the second vaccine dose (month 2) and remained seropositive for both antigens at month 12. Anti-HPV-16/18 antibody titres at month 12 remained substantially above levels associated with natural infection.** The HPV-16/18 vaccine induced sustained anti-HPV-16/18 $CD4^+$ T-cell responses in both HIV-positive and HIV-negative women. No impact of baseline $CD4^+$ T-cell count or HIV viral load was observed on the magnitude of the immune response in HIV-positive women. In HIV-positive women, $CD4^+$ T-cell count, HIV viral load and HIV clinical stage were unaffected by HPV-16/18 vaccine administration. In conclusion, the HPV-16/18 AS04-adjuvanted vaccine appears immunogenic and well-tolerated in women with HIV infection. Study ID: 107863/NCT00586339.

http://linkinghub.elsevier.com/retrieve/pii/S0264-410X(13)01273-5

Sex Transm Infect. 2013 Aug;89(5):358-65. doi: 10.1136/sextrans-2012-050685. Epub 2013 Mar 13.

High prevalence and incidence of human papillomavirus in a cohort of healthy young African female subjects.

Watson-Jones D[1], Baisley K, Brown J, Kavishe B, Andreasen A, Changalucha J, Mayaud P, Kapiga S, Gumodoka B, Hayes RJ, de Sanjosé S.

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OBJECTIVES: We measured the prevalence and incidence of human papillomavirus (HPV) infection in young female subjects recruited for a safety and immunogenicity trial of the bivalent HPV-16/18 vaccine in Tanzania.

METHODS: Healthy HIV negative female subjects aged 10-25 years were enrolled and randomised (2:1) to receive HPV-16/18 vaccine or placebo (Al(OH)3 control). At enrolment, if sexually active, genital specimens were collected for HPV DNA, other reproductive tract infections and cervical cytology. Subjects were followed to 12 months when HPV testing was repeated.

RESULTS: In total 334 participants were enrolled; 221 and 113 in vaccine and control arms, respectively. At enrolment, 74% of 142 sexually active subjects had HPV infection of whom 69% had >1 genotype. Prevalent infections were HPV-45 (16%), HPV-53 (14%), HPV-16 (13%) and HPV-58 (13%). Only age was associated with prevalent HPV infection at enrolment. Among 23 girls who reported age at first sex as 1 year younger than their current age, 15 (65.2%) had HPV infection. Of 187 genotype-specific infections at enrolment, 51 (27%) were present at 12 months. Overall, 67% of 97 sexually active participants with results at enrolment and 12 months had a new HPV genotype at follow-up. Among HPV uninfected female subjects at enrolment, the incidence of any HPV infection was 76 per 100 person-years.

CONCLUSIONS: Among young women in Tanzania, HPV is highly prevalent and acquired soon after sexual debut. Early HPV vaccination is highly recommended in this population.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23486859/

Influenza vaccine

Influenza Other Respir Viruses. 2013 Nov;7(6):1297-307. doi: 10.1111/irv.12028. Epub 2012 Nov 8.

Immunogenicity and safety of a 2009 pandemic influenza A (H1N1) monovalent vaccine in Chinese infants aged 6-35 months: a randomized, double-blind, controlled phase I clinical trial.

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OBJECTIVES: **The goal of this double-blind, randomized, controlled clinical trial was to assess the safety and immunogenicity of two different doses of a monovalent split-virion 2009 pandemic influenza A/H1N1 vaccine without adjuvant in Chinese infants aged 6-35 months.**

DESIGN AND SETTING: Subjects were randomly assigned to receive either a 2009 pandemic (H1N1) vaccine containing 7.5 or 15 μg haemagglutinin (HA) or a seasonal influenza vaccine. 2 doses of the H1N1 vaccines or the seasonal influenza vaccine were given 21 days apart in younger infants aged 6-23 months or older infants aged 24-35 months.

SAMPLE: Serum samples were collected immediately before the first injection and before and 21 days after the second injection.

MAIN OUTCOME MEASURES: Primary outcomes were haemagglutinin inhibition (HI) antibody responses 21 days following each vaccination. Safety was monitoring throughout the study.

RESULTS: **The first vaccination of 7.5 μg and 15 μg H1N1 vaccine induced seroprotective antibody titers (HI titers≥1: 40) in 42.9-57.4% of younger infants and 49.1-61.0% older infants.** Immune responses after completion of the two dose schedule were comparable in both age groups with seroprotective rates of 91-98% in each vaccine and age group and GMTs of 173-263. The H1N1 vaccine elicited similar rates of local and systemic adverse reactions as the seasonal influenza vaccine.

CONCLUSIONS: **The 2009 pandemic influenza A /H1N1 vaccine were highly immunogenic in infants aged 6-35 months, and displayed a safety and reactogenicity profile similar to the seasonal influenza vaccine.**

Hum Vaccin Immunother. 2013 Aug;9(8):1725-34. doi: 10.4161/hv.24832. Epub 2013 Jun 4.

Immunogenicity and safety of three 2010-2011 seasonal trivalent influenza vaccines in Chinese toddlers, children and older adults: a double-blind and randomized trial.

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The 2009 influenza A(H1N1) pandemic strain was for the first time included in the 2010-2011 seasonal trivalent influenza vaccine (TIV). We conducted a double-blind, **randomized trial in Chinese population to assess the immunogenicity and safety of the 2010-2011 TIV** manufactured by GlaxoSmithKline and compared it with the counterpart vaccines manufactured by Sanofi Pasteur and Sinovac Biotech. Healthy toddlers (6-36 mo), children (6-12 y) and older adults (≥60 y) with 300 participants in each age group were enrolled to randomly receive two doses (toddlers, 28 d apart) or one dose (children and older adults). The immunogenicity was assessed by hemagglutination-inhibition (HI) assay. The solicited injection-site and systemic adverse events (AEs) were collected within 7 d after vaccination. All the three TIVs were well-tolerated with 15.1% of participants reporting AEs, most of which were mild. No serious AEs and unusual AEs were reported. Fever and pain were the most common systemic and injection-site AEs, respectively. The three TIVs showed good immunogenicity. **The seroprotection rates against both H1N1 and H3N2 strains were more than 87% in toddlers after two doses and more than 95% in children and more than 86% in older adults after one dose. The seroprotection rates against B strain were 68-71% in toddlers after two doses, 70-74% in children and 69-72% in older adults after one dose**. In conclusion, the three 2010-2011 TIVs had good immunogenicity and safety in Chinese toddlers, children and older adults and were generally comparable in immunogenicity and reactogenicity.

http://www.landesbioscience.com/journals/hv/abstract.php?id=24832

Measles vaccine

Vaccine. 2013 Nov 19;31(48):5766-71. doi: 10.1016/j.vaccine.2013.08.044. Epub 2013 Aug 28.

Measles antibody levels after vaccination with Edmonston-Zagreb and Schwarz measles vaccine at 9 months or at 9 and 18 months of age: a serological study within a randomised trial of different measles vaccines.

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OBJECTIVE: Standard-titre Schwarz (SW) and Edmonston-Zagreb (EZ) measles vaccines (MV) are both used in the routine immunisation programme. **Within a trial of different strains of MV, we examined antibody responses in both one-dose and two-dose schedules when the first dose was administered at 9 months.**

SETTING AND METHODS: The trial was conducted in an urban area in Guinea-Bissau where we have had a health and demographic surveillance system and studied strategies to prevent measles infection since 1978. In the present study, **children were randomised to SW**

or EZ as the first MV and furthermore randomised to a second dose of the same MV or no vaccine at 18 months of age. We obtained blood samples from 996 children at baseline; post-vaccination blood samples were collected at 18 and 24 months of age to assess measles antibody levels after one or two doses of MV.

RESULTS: At age 18 months all had responded to the first dose and only 1% (8/699) of the children had non-protective antibody levels irrespective of vaccine type. **SW was associated with significantly higher levels of measles antibodies (geometric mean titre (GMT)=2114 mIU/mL (95%CI 1153-2412)) than EZ (GMT=807 mIU/mL (722-908)) (p=0.001).** Antibody concentration was significantly higher in girls than in boys after EZ but not after SW. Antibody levels were higher in the rainy than the dry season. There was no clear indication that a booster dose at 18 months increased the antibody level at 24 months of age.

CONCLUSIONS: **Maternal antibody levels have declined significantly in recent years and 99% had protective levels of measles antibody following primary MV at 9 months of age. It is unlikely that measles prevention and child health will be improved by increasing the age of MV as currently recommended.**

http://linkinghub.elsevier.com/retrieve/pii/S0264-410X(13)01135-3

Vaccine. 2014 Jun 17;32(29):3680-6. doi: 10.1016/j.vaccine.2014.04.031. Epub 2014 May 14.

Booster immune response in children 6-7 years of age, randomly assigned to four groups with two MMR vaccines applied by aerosol or by injection.

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IMPORTANCE: Aerosol immunization may be a useful tool to reach and sustain the elimination of measles, rubella, and congenital rubella syndrome. We compared booster seroresponses to aerosolized or injected MMR vaccines containing different strains of measles (Attenuvax or Edmonston-Zagreb) and mumps (Jeryl-Lynn or Leningrad-Zagreb).

OBJECTIVE: To assess the safety and immunogenicity of two MMR: Vaccines administered by aerosol.

METHODS: A randomized and controlled clinical trial was conducted to evaluate the safety and booster responses to the MMR SII (Serum Institute of India) and MMR II (Merck Sharp & Dhome) vaccines, both of which were administered by aerosol (ae) or injection (inj) to Mexican children aged 6-7 years in elementary schools. The seroresponses were evaluated by PRN (measles) and ELISA (rubella and mumps). Adverse events were followed-up for 28 days after the immunization.

RESULTS: Two hundred and fifty-three of 260 children completed the one-month follow-up. All participants reached protective seropositivity for measles and rubella after immunization, and 98.3 to 100% reached protective seropositivity for mumps (p=0.552). The proportions of the

seroresponses (a 2-fold rise from the baseline antibody titers) to measles were 38.3% for MMR SII (ae), 31.3% for MMR II (ae), 37.5% for MMR SII (inj), and 44.6% for MMR II (inj) (p=0.483). The seroresponses for rubella were 26.7% for MMR SII (ae), 31.3% for MMR II (ae), 46.9% for MMR SII (inj), and 40.0% for MMR II (inj) (p=0.086). **The seroresponse to mumps were 31.7% for MMR SII (ae), 25.0% for MMR II (ae), 48.4% for MMR SII (inj), and 53.9% for MMR II (inj) (p=0.002).** The difference in the seroresponse of a 4-fold rise from the baseline antibody titers was not statistically significant. Only mild adverse events were noted.

CONCLUSION: Aerosolized vaccines were as safe and as immunogenic as injected vaccines.

Comment
Seems like a premature conclusion, given that the mumps antibody seoconversion rates for injectable MMR were significantly higher than for aerosolised mumps vaccine. Other comparisons also potentially suffer from type II errors.

Clin Vaccine Immunol. 2013 Aug;20(8):1123-32. doi: 10.1128/CVI.00183-13. Epub 2013 May 29.

Effect of multivitamin supplementation on measles vaccine response among HIV-exposed uninfected Tanzanian infants.

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Immunization and nutritional interventions are mainstays of child health programs in sub-Saharan Africa, yet few published data exist on their interactions. **HIV-exposed (but uninfected) infants enrolled in a randomized placebo-controlled trial of multivitamin supplements (vitamins B complex, C, and E) conducted in Tanzania were sampled for an assessment of measles IgG quantity and avidity at 15 to 18 months.** Infants were vaccinated between 8.5 and 12 months of age, and all mothers received high-dose multivitamins as the standard of care. Of 201 HIV-exposed infants who were enrolled, 138 (68.7%) were seropositive for measles. **There were no effects of infant multivitamin supplementation on measles seroconversion proportions, IgG concentrations, or IgG avidity (P > 0.05).** The measles seroconversion proportion was greater for HIV-exposed infants vaccinated at 10 to 11 months of age than for those vaccinated at 8.5 to 10 months (P = 0.032) and greater for infants whose mothers had a CD4 T-cell count of <200 cells/μl than for infants whose mothers had a CD4 T-cell count of >350 cells/μl (P = 0.039). Stunted infants had a significantly decreased IgG quantity compared to nonstunted infants (P = 0.012). As for measles avidity, HIV-exposed infants vaccinated at 10 to 11 months had increased antibody avidity compared to those vaccinated at 8.5 to 10 months (P = 0.031). Maternal CD4 T-cell counts of <200 cells/μl were associated with decreased avidity compared to counts of >350 cells/μl (P = 0.047), as were lower infant height-for-age z-scores (P = 0.016). **Supplementation with multivitamins containing B complex, C, and E does not appear to improve measles vaccine responses for HIV-exposed infants.** Studies are needed to better characterize the impact of maternal HIV disease severity on the immune system development of HIV-exposed infants and the effect of

malnutrition interventions on vaccine responses. (This study has been registered at ClinicalTrials.gov under registration no. NCT00197730.).

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23720367/

Pneumococcal vaccine

Proc Natl Acad Sci U S A. 2014 Mar 4;111(9):3520-5. doi: 10.1073/pnas.1313748111. Epub 2014 Feb 18.

Distance to health services affects local-level vaccine efficacy for pneumococcal conjugate vaccine (PCV) among rural Filipino children.

Root ED[1], Lucero M, Nohynek H, Anthamatten P, Thomas DS, Tallo V, Tanskanen A, Quiambao BP, Puumalainen T, Lupisan SP, Ruutu P, Ladesma E, Williams GM, Riley I, Simões EA.

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Pneumococcal conjugate vaccines (PCVs) have demonstrated efficacy against childhood pneumococcal disease in several regions globally. We demonstrate how spatial epidemiological analysis of a PCV trial can assist in developing vaccination strategies that target specific geographic subpopulations at greater risk for pneumococcal pneumonia. **We conducted a secondary analysis of a randomized, placebo-controlled, double-blind vaccine trial that examined the efficacy of an 11-valent PCV among children less than 2 y of age in Bohol, Philippines.** Trial data were linked to the residential location of each participant using a geographic information system. We use spatial interpolation methods to create smoothed surface maps of vaccination rates and local-level vaccine efficacy across the study area. We then measure the relationship between distance to the main study hospital and local-level vaccine efficacy, controlling for ecological factors, using spatial autoregressive models with spatial autoregressive disturbances. We find a significant amount of spatial variation in vaccination rates across the study area. **For the primary study endpoint vaccine efficacy increased with distance from the main study hospital from -14% for children living less than 1.5 km from Bohol Regional Hospital (BRH) to 55% for children living greater than 8.5 km from BRH**. Spatial regression models indicated that after adjustment for ecological factors, distance to the main study hospital was positively related to vaccine efficacy, increasing at a rate of 4.5% per kilometer distance. **Because areas with poor access to care have significantly higher VE, targeted vaccination of children in these areas might allow for a more effective implementation of global programs.**

Comment

This is interesting, as the effectiveness of most health service interventions decreases with distance from hospitals, i.e. the population in the immediate catchment area is the best served, with worsening access and outcomes with distance from the health facility. At least in Fiji, where vaccines are widely distributed, this makes the pneumococcal vaccine a strategy that could help reverse inequity in health outcomes.

Rotavirus vaccine

Hum Vaccin Immunother. 2014 Jan;10(1):11-8. doi: 10.4161/hv.26319. Epub 2013 Sep 6.

Human rotavirus vaccine (RIX4414) efficacy in the first two years of life: a randomized, placebo-controlled trial in China.

Li RC[1], Huang T[1], Li Y[1], Luo D[2], Tao J[3], Fu B[4], Si G[5], Nong Y[1], Mo Z[1], Liao X[6], Luan I[6], Tang H[6], Rathi N[7], Karkada N[7], Han HH[8].

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[8]GlaxoSmithKline Vaccines; Philadelphia, PA USA.

Rotaviruses (RV) are a major cause of severe gastroenteritis (GE) in children aged<5 y. For the first time in China, we assessed the **efficacy of two oral doses of the human rotavirus vaccine (RIX4414) in infants during the first two years of life** (113808/NCT01171963). Healthy infants aged 6-16 weeks were randomized (1:1) to receive two oral doses of either the RIX4414 vaccine/placebo according to a 0, 1 month schedule. **Vaccine efficacy (VE) against severe RVGE was assessed from two weeks post-Dose 2 up until the end of the second RV season and calculated with its 95% confidence intervals (CI).** The primary efficacy objective was met if the lower limit of the 95% CI on VE was ≥10%. Unsolicited symptoms reported during the 31-d post-vaccination follow-up period and serious adverse events (SAEs) reported throughout the study were assessed. Of 3333 enrolled infants, 3148 were included in the according-to-protocol efficacy cohort. **Over two consecutive RV seasons, fewer severe RVGE episodes were reported in the RIX4414 group (n=21) vs. the placebo group (n=75). VE against severe RVGE was 72% (95% CI: 54.1-83.6); the lower limit of the 95% CI on VE was >10%.** The number of unsolicited symptoms and SAEs reported was similar between both groups. **Thirteen deaths (RIX4414=6; placebo=7) occurred during the study.** All SAEs and deaths in the RIX4414 group were considered unrelated to vaccination. Two oral doses of RIX4414 vaccine provided a substantial level of protection against severe RVGE in Chinese children during the first two years of life.

http://www.landesbioscience.com/journals/hv/abstract.php?id=26319

Hum Vaccin Immunother. 2013 Aug;9(8):1638-42. doi: 10.4161/hv.25076. Epub 2013 Jun 4.

Reactogenicity and safety of a liquid human rotavirus vaccine (RIX4414) in healthy adults, children and infants in China: randomized, double-blind, placebo-controlled Phase I studies.

Li RC[1], Li YP, Mo ZJ, Luo D, Huang T, Kong JL, Wang LH, Song NS, Liu A, Zhang H, Liao X, Karkada N, Han HH.

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We report the findings of three randomized, double-blind, placebo-controlled Phase I studies undertaken to support licensure of the liquid formulation of the human G1P[8] rotavirus (RV) vaccine (RIX4414; GlaxoSmithKline Biologicals SA) in China. Healthy adults aged 18-45 y (n=48) and children aged 2-6 y (n=50) received a single dose of the human RV vaccine or placebo. **Healthy infants (n=50) aged 6-16 weeks at the time of first vaccination received two oral doses of the human RV vaccine or placebo according to a 0, 1 mo schedule.** In infants, blood samples were collected prior to vaccination and one month post-dose 2 to assess anti-RV IgA antibody concentrations using ELISA. Stool samples were collected from all infants on the day of each vaccination, at 7 and 15 d after each vaccination and one month post-dose 2. Stool samples were analyzed by ELISA for detection of RV antigen to assess RV antigen excretion. **The reactogenicity profile of the human RV vaccine was found to be comparable to that of placebo in all age groups studied. The anti-RV IgA antibody seroconversion rate in infants after two vaccine doses was 86.7% (95% CI: 59.5-98.3).** Vaccine take in infants who received the liquid human RV vaccine was 86.7% (95% CI: 59.5-98.3). A Phase III efficacy study of the human RV vaccine in the infant population in China has now been completed (ROTA-075/NCT01171963).

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/23807360/

Typhoid vaccine

Cochrane Database Syst Rev. 2014 Jan 2;1:CD001261. doi: 10.1002/14651858.CD001261.pub3.

Vaccines for preventing typhoid fever.

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BACKGROUND: Typhoid fever and paratyphoid fever continue to be important causes of illness and death, particularly among children and adolescents in south-central and southeast Asia. Two typhoid vaccines are commercially available, Ty21a (oral) and Vi polysaccharide (parenteral), but neither is used routinely. Other vaccines, such as a new, modified, conjugated Vi vaccine called Vi-rEPA, are in development.

OBJECTIVES: To evaluate the efficacy and adverse effects of vaccines used to prevent typhoid fever.

SEARCH METHODS: In June 2013, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL, MEDLINE, EMBASE, LILACS, and mRCT. We also searched relevant conference proceedings up to 2013 and scanned the reference lists of all included trials.

SELECTION CRITERIA: Randomized and quasi-randomized controlled trials (RCTs) comparing typhoid fever vaccines with other typhoid fever vaccines or with an inactive agent (placebo or vaccine for a different disease).

DATA COLLECTION AND ANALYSIS: Two review authors independently applied inclusion criteria and extracted data. We computed vaccine efficacy per year of follow-up and cumulative three-year efficacy, stratifying for vaccine type and dose. The outcome addressed was typhoid fever, defined as isolation of Salmonella typhi in blood. We calculated risk ratios (RRs) and efficacy (1-RR as a percentage) with 95% confidence intervals (CIs).

MAIN RESULTS: In total, 18 RCTs were included in this review; 12 evaluated efficacy (Ty21a: five trials; Vi polysaccharide: six trials; Vi-rEPA: one trial), and 11 reported on adverse events. Ty21a vaccine (oral vaccine, three doses) **A three-dose schedule of Ty21a vaccine prevents around one-third to one-half of typhoid cases in the first two years after vaccination (Year 1: 35%, 95% CI 8% to 54%; Year 2: 58%, 95% CI 40% to 71%; one trial, 20,543 participants; moderate quality evidence; data taken from a single trial conducted in Indonesia in the 1980s).** No benefit was detected in the third year after vaccination. Four additional cluster-RCTs have been conducted, but the study authors did not adjust for clustering.Compared with placebo, this vaccine was not associated with more participants with vomiting, diarrhoea, nausea or abdominal pain (four trials, 2066 participants; moderate quality evidence) headache, or rash (two trials, 1190 participants; moderate quality evidence); however, fever (four trials, 2066 participants; moderate quality evidence) was more common in the vaccine group. Vi polysaccharide vaccine (injection, one dose) **A single dose of Vi polysaccharide vaccine prevents around two-thirds of typhoid cases in the first year after vaccination (Year 1: 69%, 95% CI 63% to 74%; three trials, 99,979 participants; high quality evidence).** In Year 2, the trial results were more variable, with the vaccine preventing between 45% and 69% of typhoid cases (Year 2: 59%, 95% CI 45% to 69%; four trials, 194,969 participants; moderate quality evidence). The three-year cumulative efficacy of the vaccine is around 55% (95% CI 30% to 70%; 11,384 participants, one trial; moderate quality evidence). These data are taken from a single trial in South Africa in the 1980s.Compared with placebo, this vaccine was not associated with more participants with fever (four trials, 133,038 participants; moderate quality evidence) or erythema (three trials, 132,261 participants; low quality evidence); however, swelling (three trials, 1767 participants; moderate quality evidence) and pain at the injection site (one trial, 667 participants; moderate quality evidence) were more common in the vaccine group. Vi-rEPA vaccine (two doses) Administration of two doses of the Vi-rEPA vaccine prevents between 50% and 96% of typhoid cases during the first two years after vaccination (Year 1: 94%, 95% CI 75% to 99%; Year 2: 87%, 95% CI 56% to 96%; one trial, 12,008 participants; moderate quality evidence). These data are taken from a single trial with children 2 to 5 years of age conducted in Vietnam.Compared with placebo, the first and second doses of this vaccine were not associated with increased risk of adverse events. The first dose of this vaccine was not associated with fever (2 studies, 12,209 participants; low quality evidence), erythema (two trials, 12,209 participants; moderate quality evidence) or swelling at the injection site (two trials, 12,209 participants; moderate quality evidence). The second dose of this vaccine was not associated with fever (two trials, 11,286 participants; low quality evidence), erythema (two trials, 11,286 participants; moderate quality evidence) and swelling at the injection site (two trials, 11,286 participants; moderate quality evidence).

AUTHORS' CONCLUSIONS: **The licensed Ty21a and Vi polysaccharide vaccines are efficacious.** The new and unlicensed Vi-rEPA vaccine is as efficacious and may confer longer immunity.

http://onlinelibrary.wiley.com/store/10.1002/14651858.CD001261.pub3/asset/CD001261.pdf?v=1&t=hxd4g6gy&s=e51a97a38958cf8478a0c0d8f21bea6a8942420d

Lancet Infect Dis. 2014 Feb;14(2):119-29. doi: 10.1016/S1473-3099(13)70241-X. Epub 2013 Nov 28.

Immunogenicity and safety of the Vi-CRM197 conjugate vaccine against typhoid fever in adults, children, and infants in south and southeast Asia: results from two randomised, observer-blind, age de-escalation, phase 2 trials.

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BACKGROUND: Typhoid vaccination is a public health priority in developing countries where young children are greatly affected by typhoid fever. Because present vaccines are not recommended for children younger than 2 years, the Novartis Vaccines Institute for Global Health developed a conjugate vaccine (Vi-CRM197) for infant immunisation. We aimed to assess the immunogenicity and safety of Vi-CRM197 in participants of various ages in endemic countries in south and southeast Asia.

METHODS: We did two randomised, observer-blind, age de-escalation, phase 2 trials at two sites in Pakistan and India (study A), and at one site in the Philippines (study B), between March 2, 2011, and Aug 9, 2012. Adults aged 18-45 years, children aged 24-59 months, older infants aged 9-12 months, and infants aged 6-8 weeks were randomly assigned (1:1) with a computer-generated randomisation list (block size of four) to receive either 5 μg Vi-CRM197 or 25 μg Vi-polysaccharide vaccine (or 13-valent pneumococcal conjugate vaccine in children younger than 2 years). Both infant populations received Vi-CRM197 concomitantly with vaccines of the Expanded Programme on Immunization (EPI), according to WHO schedule. With the exception of designated study site personnel responsible for vaccine preparation, study investigators, those assessing outcomes, and data analysts were masked to treatment allocation. We specified no a-priori null hypothesis for the immunogenicity or safety objectives and all analyses were descriptive. Analyses were by modified intention-to-treat. These studies are registered with ClinicalTrials.gov, numbers NCT01229176 and NCT01437267.

FINDINGS: 320 participants were enrolled and vaccinated in the two trials: 200 in study A (all age groups) and 120 in study B (children and infants only), of whom 317 (99%) were included in the modified intention-to-treat analysis. **One dose of Vi-CRM197 significantly increased concentrations of anti-Vi antibody in adults (from 113 U/mL [95% CI 67-190] to 208 U/mL [117-369]), children (201 U/mL [138-294] to 368 U/mL [234-580]), and older**

infants (179 U/mL [129-250] to 249 U/mL [130-477]). However, in children and older infants, a second dose of conjugate vaccine had no incremental effect on antibody titres and, at all ages, concentrations of antibodies increased substantially 6 months after vaccination (from 55 U/mL [33-94] to 63 U/mL [35-114] in adults, from 23 U/mL [15-34] to 51 U/mL [34-76] in children, and from 21 U/mL [14-31] to 22 U/mL [14-33] in older infants). **Immune response in infants aged 6-8 weeks was lower than that in older participants and, 6 months after third vaccination, antibody concentrations were significantly higher than pre-vaccination concentrations in Filipino (21 U/mL [16-28] vs 2.88 U/mL [1.95-4.25]), but not Pakistani (3.76 U/mL [2.77-5.08] vs 2.77 U/mL [2.1-3.66]), infants.** Vi-CRM197 was safe and well tolerated and did not induce any significant interference with EPI vaccines. No deaths or vaccine-related serious adverse events were reported throughout the studies.

INTERPRETATION: **Vi-CRM197 is safe and immunogenic in endemic populations of all ages.** Given at 9 months of age, concomitantly with measles vaccine, Vi-CRM197 shows a promise for potential inclusion in EPI schedules of countries endemic for typhoid. An apparent absence of booster response and a reduction in antibody titres 6 months after immunisation should be further investigated, but data show that an immunogenic typhoid vaccine can be safely delivered to infants during EPI visits recommended by WHO.

Expert Rev Vaccines. 2013 Nov;12(11):1273-86. doi: 10.1586/14760584.2013.845529.

Development of Vi conjugate - a new generation of typhoid vaccine.

Szu SC.

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Typhoid fever remains to be a serious disease burden worldwide with an estimated annual incidence about 20 million. The licensed vaccines showed moderate protections and have multiple deficiencies. Most important of all, none of the licensed typhoid vaccines demonstrated protection for children under 5 years old. These limitations impeded successful implementation of typhoid vaccination programs. To improve immunogenicity Vi was conjugated to rEPA, a recombinant exoprotein A from Pseudomonas aeruginosa. Vi-rEPA showed higher and longer lasting anti-Vi IgG in adults and children than Vi alone in high endemic areas. In school-age children and adults, the immunity persisted more than 8 years. **In a double-blind, placebo-controlled and randomized efficacy trial in 2- to 5-year-old children, Vi-rEPA conferred 89% protective efficacy against typhoid fever and the protection lasted at least 4 years. When given concomitantly with infant routine vaccines, Vi-rEPA was safe, immunogenic and showed no interference with the routine vaccines.** Vi conjugate vaccine was also attempted and successfully demonstrated by several other laboratories and manufactures. Using either rEPA or different carrier proteins, such as diphtheria or tetanus toxoid, recombinant diphtheria toxin (CRM197), the Vi conjugates synthesized was significantly more immunogenic than Vi alone. Recently, two Vi-tetanus toxoid conjugates were licensed in India for all ages, starts as young as 3 month old. This new generation of typhoid vaccine opens up a new era for typhoid prevention and elimination.

Vitamin A

(See also Maternal health, nutrition and micronutrient supplementation, HIV prevention of mother to child transmission)

J Nutr. 2014 Apr;144(4):519-24. doi: 10.3945/jn.113.182998. Epub 2014 Feb 5.

Triple-fortified rice containing vitamin A reduced marginal vitamin A deficiency and increased vitamin A liver stores in school-aged Thai children.

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Vitamin A (VA)-fortified rice is a potential intervention strategy to prevent VA deficiency in at-risk populations. **Hot-extruded, triple-fortified rice grains with added VA, zinc, and iron were produced by hot extrusion technology and their ability to improve VA status was tested in Thai schoolchildren.** The fortification levels were 10 mg of iron, 9 mg of zinc, and 1.05 mg of VA/g extruded rice. A paired stable isotope dilution technique with labeled $^{13}C_2$-retinyl acetate (^{13}C-RID) was used to quantify VA pool size at the beginning and end of the feeding period. **Fifty healthy schoolchildren with a serum retinol (SR) concentration of >0.7 μmol/L were randomly assigned to 2 groups to receive either triple-fortified rice (n = 25) or natural rice (n = 25) for 2 mo as part of the daily school meal. The fortified grains, mixed 1:50 with regular rice, were estimated to provide an extra 890 μg of VA/d, 5 d/wk. $^{13}C_2$-retinyl acetate (1.0 μmol) was administered orally to each child before and at the end of the feeding period to estimate total body reserves (TBRs) of VA, which increased significantly (P < 0.05) in the intervention group from 153 ± 66 μmol retinol at baseline to 269 ± 148 μmol retinol after 2 mo of feeding.** There was no change in the TBRs of VA in the control group (108 ± 67 vs. 124 ± 89 μmol retinol) (P = 0.22). Serum retinol remained unchanged in both groups. We conclude that VA-fortified, hot-extruded rice is an efficacious vehicle to provide additional VA to at-risk populations, and that the efficacy of VA-fortified foods can be usefully monitored by the ^{13}C-RID measurement of TBRs of VA but not by changes in SR concentration.

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Effects of vitamin A supplementation on iron status indices and iron deficiency anaemia: a randomized controlled trial.

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Iron deficiency anaemia (IDA) is the most common nutritional deficiency in the world including developed and developing countries. Despite intensive efforts to improve the quality of life of rural and aboriginal communities in Malaysia, anaemia and IDA are still major public health problems in these communities particularly among children. **A randomized, double-blind,**

placebo-controlled trial was conducted on 250 Orang Asli (aboriginal) schoolchildren in Malaysia to investigate the effects of a single high-dose of vitamin A supplementation (200,000 IU) on iron status indices, anaemia and IDA status. The effect of the supplement was assessed after 3 months of receiving the supplements; after a complete 3-day deworming course of 400 mg/day of albendazole tablets. The prevalence of anaemia was found to be high: 48.5% (95% CI=42.3, 54.8). Moreover, 34% (95% CI=28.3, 40.2) of the children had IDA, which accounted for 70.1% of the anaemic cases. The findings showed that **the reduction in serum ferritin level and the increments in haemoglobin, serum iron and transferrin saturation were found to be significant among children allocated to the vitamin A group compared to those allocated to the placebo group ($p<0.01$). Moreover, a significant reduction in the prevalence of IDA by almost 22% than prevalence at baseline was reported among children in the vitamin A group compared with only 2.3% reduction among children in the placebo group.** In conclusion, vitamin A supplementation showed a significant impact on iron status indices and IDA among Orang Asli children. Hence, providing vitamin A supplementation and imparting the knowledge related to nutritious food should be considered in the efforts to improve the nutritional and health status of these children as a part of efforts to improve the quality of life in rural and aboriginal communities.

http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/24384995/

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Effect of simultaneous supplementation of vitamin A and iron on diarrheal and respiratory tract infection in preschool children in Chengdu City, China.

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OBJECTIVE: The goal of this study was to investigate whether vitamin A combined with iron supplementation for preschool children resulted in improved changes in children's infectious morbidity.

METHOD: In this randomized placebo-controlled and blinded field intervention trial, totally 445 preschoolers, ages 3 to 6 y old, were randomly selected. All children were randomly divided into four groups: **vitamin A supplement-only group (group I), iron supplement-only group (group II), vitamin A and iron supplement group (group III), and no vitamin A and ferrous sulfate as placebo-control (group IV) for 6 mo.** The morbidity of diarrhea and respiratory infections, were collected during supplementation.

RESULTS: There was evidence of the lowest incidence rate of respiratory-related illnesses and fewest symptoms of runny nose, cough, and fever for children in group III compared with children in groups I, II and IV ($P < 0.05$). Moreover, despite the undistinguished incidence rate of vomiting, nausea, and stomach pain, the rate of diarrhea-related illness was significantly lower for children in group III than for those in the other three groups.

CONCLUSION: **The beneficial affects on infectious morbidity over 6 mo, highlight the potential of vitamin A plus an iron supplement for preschool-aged children**.

Vitamin D

(See Tuberculosis, and Endocrine disorders and bone health)

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Impact of vitamin D fortified milk supplementation on vitamin D status of healthy school children aged 10-14 years.

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Vitamin D deficiency is a major public health problem, needing immediate attention. We studied the effect of vitamin D fortification of milk in school children. Our results show that fortification of milk is safe and effective strategy to deal with widespread vitamin D deficiency.

INTRODUCTION: Vitamin D deficiency among school children and adolescents is a well-documented major public health problem, needing immediate attention. To assess the effect of vitamin D fortified milk on serum 25 hydroxy vitamin D [S.25(OH)D] levels, we carried out a prospective double-blind randomized control trial in apparently healthy school children, aged 10-14 years.

METHODS: Of 776 subjects recruited out of 796 who consented, 713 (boys-300; girls-413) completed the study. Subjects were randomized into three groups. **Group A (n = 237) received 200 ml of unfortified milk per day while group B (n = 243) and group C (n = 233) received 200 ml of milk fortified with 600 IU (15 µg) and 1,000 IU (25 µg) of vitamin D per day for 12 weeks.** Serum calcium, phosphate, alkaline phosphatase, S.25(OH)D, and urinary calcium/creatinine ratio were estimated at baseline and after supplementation.

RESULTS: Hypovitaminosis D [25(OH)D < 20 ng/ml] was observed in 92.3 % subjects with mean S.25(OH)D level of 11.69 ± 5.36 ng/ml. **There was no significant difference in S.25(OH)D levels among the three groups at baseline.** The mean percentage change in S.25(OH)D level in groups B (137.97 %) and C (177.29 %.) were significantly greater than group A (-5.25 %). **The percentage of subjects having S.25(OH)D levels >20 ng/ml following supplementation were 5.9 % in group A, 69.95 % in group B, and 81.11 % in group C in comparison to 6.32 %, 4.9 % and 12 %, respectively, at baseline.**

CONCLUSION: Fortification of milk with vitamin D is an effective and safe strategy in improving S.25(OH)D levels in children aged 10-14 years.

Zinc

(see also: Acute respiratory infection, Diarrhoea, Nutrition – micronutrients, Vitamin A, Cholera vaccine)

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Absorbed zinc and exchangeable zinc pool size are greater in Pakistani infants receiving traditional complementary foods with zinc-fortified micronutrient powder.

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Adequacy of zinc intake from breast milk alone becomes marginal in relation to infant requirements by around 6 mo of age. Simple and cost-effective strategies are needed at the population level to ensure adequate intakes of zinc in infants and toddlers in populations at risk of zinc deficiency. **We determined the amount of absorbed zinc (AZ) from a micronutrient powder (MNP) without and with 10 mg of zinc (MNP+Zn) added to local complementary foods used in Pakistan and the impact on the exchangeable zinc pool (EZP) size.** As a nested study within a large, prospective, cluster randomized trial, **6-mo-old infants were randomly assigned to receive MNP or MNP+Zn.** Stable isotope methodology was applied after ~3 and 9 mo of use to measure AZ from MNP-fortified test meals of rice-lentils (khitchri) and EZP. Nineteen infants per group completed the first metabolic studies and 14 and 17 infants in the MNP and MNP+Zn groups, respectively, completed the follow-up studies. AZs were (mean ± SD) 0.1 ± 0.1 and 1.2 ± 0.5 mg at the first point for the MNP and MNP+Zn groups, respectively ($P < 0.001$); results were nearly identical at the follow-up measurement. **EZP did not differ between groups at the first measurement but was less in the MNP group (3.7 ± 0.6 mg/kg) than in the MNP+Zn group (4.5 ± 1.0 mg/kg) at the second measurement ($P = 0.01$).** These data confirm that the MNP+Zn in khitchri were well absorbed and after 1 y of home fortification, zinc status assessed by EZP was significantly better for the MNP+Zn group. Additional field studies may be necessary to ascertain the adequacy of this dose for infants at high risk of deficiency. This trial was registered at ClinicalTrials.gov as NCT00705445.

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Associations between intestinal mucosal function and changes in plasma zinc concentration following zinc supplementation.

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OBJECTIVES: Subclinical **environmental enteropathy** is associated with malabsorption of fats, carbohydrates, and vitamins A, B12, and folate; however, little information is available on mineral absorption. We therefore investigated the relation between intestinal mucosal function (measured by the lactulose:mannitol permeability test and plasma citrulline concentration), and zinc (Zn) absorption, as estimated by the change in plasma Zn concentration (PZC) following short-term Zn or placebo supplementation.

METHODS: We conducted a randomized, partially masked, placebo-controlled trial among **282 apparently healthy children 6 to 23 months of age in Burkina Faso. After completing baseline intestinal function tests, participants received either 5 mg Zn, as zinc sulfate, or placebo, daily for 21 days.**

RESULTS: At baseline, mean ± standard deviation PZC was 62.9 ± 11.9 μg/dL; median (interquartile range) urinary lactulose:mannitol (L:M) recovery ratio and plasma citrulline concentrations were 0.04 (0.03-0.07) and 11.4 (9.0-15.6) μmol/L, respectively. Change in PZC was significantly greater in the Zn-supplemented versus placebo group (15.6 ± 13.3 vs 0.02 ± 10.9 μg/dL; P < 0.0001), and was negatively associated with initial urinary L:M recovery ratio (-1.1 μg/dL per 50% increase in urinary L:M recovery ratio; P = 0.014); this latter relation did not differ between supplementation groups (P = 0.26). Baseline plasma citrulline concentration was not associated with change in PZC.

CONCLUSIONS: **Although altered intestinal permeability may reduce dietary Zn absorption, it likely does not undermine the efficacy of Zn supplementation, given the large increases in PZC following short-term Zn supplementation observed in this study, even among those with increased urinary L:M recovery ratios.**